University of Alberta

Mental and Health-Related Quality of Life outcomes in children post-liver transplant

by

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Dedication

To Douglas, Kate, Harry and Jennifer for all your support and love.

To all our wonderful patients and families who took time to participate as well as express their support of this endeavor to assist the transplant children of the future.

Abstract

Outcomes research in pediatric liver transplant has focused on mortality and surgical morbidity but there is an increasing awareness of the need to evaluate functional outcomes, including developmental/cognitive status and health-related quality of life (HRQOL).

Methods: Standardized developmental/cognitive testing and a validated HRQOL measures were administered to a cohort of children transplanted at the University of Alberta. Practice variables potentially associated with developmental/cognitive delay and diminished HRQOL were analyzed.

Results: Developmental/cognitive delay was demonstrated in 54% of the cohort. Variables predictive of delay were different for performance (PIQ) or verbal IQ (VIQ) impairment. Diminished PIQ was associated with impaired growth and pre-transplant hyperammonemia and diminished VIQ was associated with elevated serum levels of immunosuppressive medications. HRQOL was diminished compared to a reference cohort, with more affected attributes.

Conclusion: Children who have undergone pediatric liver transplantation have impaired developmental/cognitive function and diminished HRQOL.

Table of Contents

Chapter 1:	**Introduction**	
	1.1 Introduction	**2**
Chapter 2:	**Literature Review**	
	2.1 Search Strategy	**11**
Chapter 3:	**Objectives**	
	3.1 General Research Objectives	**31**
	3.2 Specific Research Objectives	**31**
Chapter 4:	**Objectives 1 & 2**	
	4.1 Methods	**34**
	4.2 Results	**42**
	4.3 Discussion	**63**
Chapter 5:	**Objectives 3 & 4**	
	5.1 Methods	**72**
	5.2 Results	**80**
	5.3 Discussion	**88**
Chapter 6:	**Conclusions & Recommendations**	
	6.1 Conclusions	**94**
	6.2 Recommendations for Future Research	**97**
Bibliography		**101**
Appendix A		**106**
Appendix B		**119**

List of Tables

Table 2.1	Summary of studies examining the developmental/cognitive delay associated with childhood liver transplant	17
Table 2.2	Summary of studies examining pediatric Health-related quality of life post-liver transplant	27
Table 4.1	Summary of the applicable age ranges, subtesting & standardized information for standardized measures	39
Table 4.2	Descriptive characteristics of all study participants	44
Table 4.3	Descriptive pre-transplant variables of 30 assessed & 12 not assessed children after liver transplant at < 6 years of age: n (%), mean $\pm$ SD	45
Table 4.4	Pre- and post-transplant variables for 30 assessed younger and older children after liver transplantation at < 6 years of age: n (%), mean $\pm$ SD	46
Table 4.5	Psychological test results for 30 assessed younger and older children after liver transplantation at < 6 years of age: mean $\pm$ SD	46
Table 4.6	School achievement scores of 11 children after liver transplant at < 6 years of age: mean $\pm$ SD, n (%)	53
Table 4.7	Univariate regression analysis (variables with $p < 0.2$)	59
Table 4.8	Dichotomous variables, t-test for gender and outcome variables	60
Table 4.9	Dichotomous variables, t-test for diagnosis (Biliary atresia/other) and outcome variables	61
Table 4.10	Multiple regression analysis for predictive variables and dependent outcomes	62
Table 5.1	Multi-attribute Health Status classification system	76

Table 5.2	**Patient characteristics for health related quality of life study**	**82**
Table 5.3	**Practice variables of participants (n=20)**	**83**
Table 5.4	**% abnormal score on the Multi-attribute Health Status classification system of 20 children after liver transplant at < 6 years of age, n (%), compared with a reference population**	**85**
Table 5.5	**Frequencies of number of attributes affected in liver transplant survivors and reference subjects**	**86**

List of Figures

Figure 4.1	**Sample scatter plot and regression line for univariate analysis, Beery and serum ammonia**	**57**
Figure 4.2	**Sample scatter plot and regression line for univariate analysis, Performance intelligence quotient and height percentile**	**58**

List of Abbreviations

CLD:	**Chronic liver disease**
CNS:	**Central nervous system**
UNOS:	**United Network of Organ Sharing**
SES:	**Socioeconomic status**
IQ:	**Intelligence quotient**
DQ:	**Developmental quotient**
FSIQ:	**Full scale score intelligence quotient**
DQ/FSIQ:	**Combined development quotient and full scale intelligence**
quotient	
PIQ:	**Performance intelligence quotient**
VIQ:	**Verbal intelligence quotient**
BSID II:	**Bayley Scales of Infant Development-Second edition**
MDI:	**Mental developmental index**
PDI:	**Motor developmental index**
WPPSI – R:	**Wechsler Preschool and Primary scales of Intelligence –**
revised	
WISC III:	**Wechsler Intelligence Score for Children-Third edition**
WIAT:	**Wechsler Individual Achievement Tests**
VABS:	**Vineland Adaptive Behavioral Scales**
VMI:	**Visual motor integration**
HRQOL:	**Health Related Quality of Life**
QOL:	**Quality of Life**
MAHS:	**Multi-attribute health status**
HUI:	**Health utilities index**
CHQ-50:	**Child Health Questionnarie-50**
Peds QL 4.0:	**Pediatric Quality of Life-version 4.0**
ELBW:	**Extreme low birth weight**
CI:	**Calcineurin inhibitors**

Chapter 1

Introduction

1.1 Introduction

Since 1983, liver transplant has been considered non-experimental standard therapy for end-stage liver disease. It is now the treatment of choice for children with end-stage liver disease who otherwise do not have bridging therapy alternatives, such as dialysis or extracorporeal membrane devices. Currently 10% - 15% of all liver transplants are performed in pediatric patients (UNOS, 2002). Dramatic gains in post-transplant survival has occurred over the past decade due to innovations in surgical technique including the use of segments of adult donor livers, living donation, and split liver transplant (sharing a graft between a child an adult recipient); improved post-operative care; and better immunosuppressive regimes. Children who previously would have died from their liver failure now have a 75%-90% chance of long-term survival with a liver transplant (Wallot, 2002).

Despite the advances in this therapy, most literature assessing pediatric outcomes post-liver transplant has been directed to mortality and transplant specific morbidity with little research into outcomes such as neurodevelopment, school performance and health related quality of life (HRQOL). To date there has been a paucity of literature on the humanistic outcomes as part of the assessment of many new technologies, including liver transplant (Hack, 1999). Assessing functional outcomes incorporates the realization that a child with a complex chronic condition is not a disease in isolation but rather a developing child who is part of a family unit and interacts with peers and school systems. Outcomes data provides information upon

which the medical community and individual families can assess the potential benefit and impact of highly invasive technologies. This information can only be complete when there is documentation of development, cognition, school performance and quality of life.

Previous literature has demonstrated that different chronic pediatric illnesses can result in mental deficits (Berg 1989). Cognitive ability is the cornerstone of many functional outcomes in children. Cognitive function is defined as the child's ability to receive, evaluate, respond and to retain new information and can be regarded as the basis for adaptive potential (Tarter 1988). Therefore, impaired cognitive ability broadly impacts upon the lives of children, affecting their school performance, socialization, peer and family interactions. These are fundamental elements of the child's existence. Poor cognitive function has been associated with a decreased quality of life as measured with valid generic instruments (Adeback, 2003).

Cognitive/developmental function represents the culmination of multiple factors: genetic potential, environment, physical health status and an intact neurological status. Children with infantile onset liver disease are at extremely high risk for neurological impairment resulting in mental deficits. Infancy is a time of rapid neural growth therefore negative influences, such a chronic liver disease, can have a profound negative effect on a child's developmental/cognitive potential. Neural growth is most rapid in the first year of life due to glial proliferation and myelination of the central nervous system (CNS). Specifically between 3 and 10 months of age, CNS growth spurts account for 30% of brain growth (Epstein 1978).

During these early months end-stage liver disease may be well established, resulting in abnormal CNS development.

Children who survive the pre- and post-transplant period are exposed to multiple factors that have the potential to negatively impact on functional outcomes, including cognition and quality of life. It is important to demonstrate whether the hypothesis that neurological insults from the pre- and post-transplant period do result in an increased prevalence of developmental/cognitive delay and impaired quality of life is true. Once this hypothesis has been demonstrated the next step is to delineate the variables of end-stage liver disease and/or liver transplantation that result in neurologic deficits. Identifying predictive variables may initiate change in the clinical management and subsequently improve long-term outcome (Adeback 2003).

Previous literature has supported the hypothesis that neurological, developmental/cognitive and quality of life deficits do occur in the pediatric liver transplant population. Developmental/cognitive deficits have been found in 25%-60% of children post-liver transplant (Stewart 1989, Wayman 1997). Neurological complications have been reported in 30%-60% of all solid organ transplant recipients (Patchell 1994), and quality of life has been demonstrated to be lower than in general pediatric populations (Alonso 2003, Bucuvalus 2003). Some hypotheses as to the potential causes of neurological complications and the resultant developmental/cognitive deficits have included metabolic derangements, malnutrition and adverse events due to medication.

Prior to transplantation, chronic liver disease (CLD) may be associated with reversible and permanent neuropathology findings. Autopsy series reveal over 80% of patients with CLD exhibited abnormal neuropathology. Clinically, one of the hallmarks of liver failure's metabolic derangements is encephalopathy. Encephalopathy is staged from I to V, with stage I exhibiting slow mentation, irritability and sleep disturbance to stage V which is an unarousable coma with apnea. The pathogenesis is still not known but research has focused on four hypotheses; ammonia accumulation, synergistic neurotoxins, false neurotransmitters and gamma-aminobutyric acid inhibiting neurotransmitters. Most changes in mentation are reversible with improved liver function but permanent effects may occur (Treem, 2000).

Chronic liver disease also results in decreased coagulation factors which are synthesized in the liver. The clinical manifestation of this is a markedly decreased ability to clot. Delayed clotting can also be affected by the thrombocytopenia secondary to hypersplenism. These abnormalities in the coagulation cascade may result in intracerebral hemorrhage (Patchell, 1994).

In addition, CLD is associated with malnutrition secondary to many factors including anorexia of chronic disease, increased metabolic rate and decreased intake secondary to the mechanical factors of ascites and organomegaly. Cholestasis with impaired bile flow and bile salt flow results in an inability to form micelles necessary to absorb dietary fat and fat-soluble vitamins, compounding the malnutrition. As noted previously, neural growth is most rapid in the early years of life so that lack of nutrients has a profound effect upon brain growth and development in early life.

Research has demonstrated that malnutrition during the first two years of life can result in permanent changes in brain architecture. (Granthum-McGregor 1995) Several case-control studies have demonstrated malnourished children have decreased school performance and decreased global IQ. Perceptual-spatial function appears to be the most impaired domain (Epstein 1978).

Medications used post-transplant are one of the most common documented causes of neurological insult post solid organ transplant. Calcineurin inhibitors, notably cyclosporin and tacrolimus, have direct neurotoxic side-effects. These medications are utilized in the immediate post-transplant period and for life-long maintenance of immunosuppression to prevent graft rejection. In reported adult series, 15%-40% of patients experience neurological side-effects, with motor syndromes, most notably tremor, being common. Encephalopathy occurring in 5% of patients is the most severe side-effect of these medications. These medications are also epileptogenic. Neuroimaging by MRI may reveal cerebral leukoenephalopathy secondary to calcineurin inhibitors (Patchell 1994).

Systemic corticosteroids are also utilized in the immediate post-transplant period and for a variable amount of time post-transplant. High dose pulse corticosteroids are considered first-line therapy for graft rejections. Adverse effects on neural growth and memory have been documented with the utilization of these medications (Keenan 1996). Many studies have examined the effect of corticosteroids on both long and short-term use on cognitive function. The most consistent finding has been on the detrimental effect on memory, especially explicit

memory. Other studies have isolated this affect to a negative impact on hippocampal function (Keenan 1996).

Decreased immunosurveillence, secondary to these immunosuppressing medications, results in an increased risk for central nervous system (CNS) infections such as intracerebral abscesses. Another ominous post-transplant infection is that of Ebstein Barr virus (EBV). Decreased T cell function can result in EBV-induced lymphomas. This post-transplant lymphoproliferative disease has been well documented to have CNS involvement and previous treatment has included cranial irradiation (Patchell 1994).

Not only do these children have significant physical health issues pre- and post-transplant they also have complex psychosocial issues secondary to the families and children emotionally coping with a previous fatal illness and now the chronic illness of immunosuppression. They may also exhibit residual psychological issues from the peri-operative period and intensive care environment. Since health-related quality of life (HRQOL) is determined by health-related factors, such as physical well-being, social/emotional functioning, mental and psychological status, one can easily observe how the child and family's HRQOL may be adversely affected by liver transplantation.

Over 650 pediatric transplants are performed each year in North America (UNOS 2002), many of which are performed on infants and very young children with chronic liver disease who are at high risk for developmental/cognitive and HRQOL impairment. Despite this great number, there have only been 7 small cohort studies

examining developmental/cognitive outcomes (Schultz 2003, Adeback 2003, Krull 2003, Gritti 2001, Kennard 1999, Wayman 1997, Stewart 1989) and four liver transplant cohort studies reporting health related quality of life based on a validated measure (Alonso 2003, Bucuvalus 2003, Schultz 2003, Midgley 2000). The studies examining developmental/cognitive outcomes demonstrated that 10%-60% of children were delayed or borderline delayed. The studies examining HRQOL utilized the Health Utilities Index II, the Child Health Questionnaire and the Pediatric Quality of Life Questionnaire (Peds-QL). All of the questionnaires revealed a moderately decreased HRQOL versus population normative data. Further and more detailed information on a larger number of children is required to influence clinical practice patterns so that improved cognitive and quality of life outcomes can be achieved.

Developmental/cognitive function is measured using population standardized and validated educational psychology measures. The utilization of such measures allows for objective and interpretable information and provides a more accurate picture of children's outcomes post-liver transplantation. Much of the early transplant literature, and still some current publications, equate developmental/cognitive outcomes with school attendance, parents perception of cognitive performance or repetition of a grade (Zitelli 1988, Gritti 2001). Although this information is useful to assess some functional outcomes post-transplant it does not provide direct information of cognitive performance. This lack of information is for many reasons. First there is a poor correlation between grades assigned in school and cognitive ability (Wechsler, 1981). Second, the parental reports are biased by parent's perception and expectations of their child. These expectations may be much lower

than for age matched peers because they may perceive their child as sick and are grateful that they are living and do not expect normal developmental milestones/cognitive performance. Third, the policy of grade repetition varies with school districts. And finally, many children who have learning problems are not recognized in the school system. By defining developmental/cognitive ability based upon special education requirements the number of children with developmental/cognitive impairment is underestimated. Studies objectively examining cognitive/school performance found that the majority of post-transplant children with learning deficits are not being identified and do not receive the special education that they required (Kennard 1999).

Advances in medical technology, such as liver transplant, provide hope for children with liver failure. But we must also adequately assess the impact of this technology on the broader determinants of child health, including neurological, cognitive development, and health related quality of life. Understanding the learning profile of the children provides information needed to ensure ongoing educational and societal support to help individual children achieve their maximum potential. Children's maximum potential can only occur when we objectively assess outcomes, critique our current pre- and post-transplant management and are prepared to modify therapy to improve their lives.

Chapter Two

Literature Review

2.1 Search Strategy

Literature searches were conducted utilizing computerized databases: PubMed; Medline; and EMBASE. Three methods were used to insure that all references were reviewed. First, the initial search was conducted on pediatric liver transplant and the area of interest (developmental/cognitive delay, HRQOL). Second, bibliographies of the eligible papers were hand reviewed to insure that no previous literature was missed. Third, Web of Science was utilized to cross-reference the eligible studies to insure that all appropriate references were included. The Web of Science query yielded 81 citations, all of which had been noted in the other search strategies.

2.1.1

The search strategy for developmental/cognitive delay yielded 474 citations. After reviewing the abstracts, only 12 abstracts appeared to meet the inclusion criteria stated below and when these were reviewed only eight papers were found to be eligible. Papers were included if they met the three criteria. First, only studies examining pediatric liver transplant recipients in isolation were included. Papers that included all solid organ recipients (heart, lung, kidney, and liver) as one group were not included. Second, studies must have included children with chronic-end stage liver disease and not only children with fulminant failure. Finally, the papers had to have used standardized and well-accepted measures of development/cognition.

Descriptions of grade placement and parent/self reports of development/cognitive ability were not accepted.

Only eight papers fulfilled the outlined criteria. Six papers by Stewart were based on the same cohort, as evidenced by the same number of patients with the same number in each diagnostic category. (Stewart 1987, Stewart 1989, Stewart 1991, Stewart 1991, Stewart 1992, Stewart 1994) Two authors, Stewart and Kennard are from the same institution but Kennard had a larger cohort. Therefore only two papers were referenced, the initial study and the most recent which had a larger cohort. (Stewart 1989, Kennard 1999)

A summary of the developmental/cognitive delay eligible articles is presented in table 2.1. The table describes the study subjects' demographics, follow-up period and number of eligible and participating patients. The table also provides a summary of the results of the studies, including the measures used, the scores of the measurements used, statistical tests used , and if the authors evaluated or found any predictive variables for any developmental/cognitive delay demonstrated.

The liver transplant cohort from Children's Medical Centre, Dallas, was one of the first published cohorts providing an extensive and objective assessment of the developmental/cognitive outcomes post-transplantation. This cohort was initially described by Stewart in 1989 and then further studied with some more patients in 1999 (Kennard, 1999). The authors used standard, validated measures. This work was important because it was one of the first to objectively demonstrate that many children post-liver transplant had delay with a full-scale intelligence quotient (FSIQ)

greater than two standard deviations from the population norm (FSIQ < 70), which is the clinical definition of cognitive delay. Many others were borderline delayed, FSIQ between -1 to –2 standard deviations (SD) (FSIQ 84-70). Stewart and Kennard defined borderline delay as between –1 to –2 standard deviations from the normative mean, as those children will require enhanced learning environments. Educational psychologists may further subdivide this group into DQ/FSIQ 80-89, low average and 70-79 as borderline delayed. Kennard also described the academic achievement of this cohort with the Woodcock-Johnson Educational Test Battery-revised. This provided information in the areas of reading, written language and math. This further illustrated that many children had discrepancies between the FSIQ and their subject achievement scores. Almost half of the cohort, 22/50, scored lower in at least one subject area than would have been predicted based on the FSIQ. It was noted that all the children who met the definition of delay (FSIQ < 70) were receiving special education, of the children with a FSIQ 84-70 only 38% receiving special tuition. Therefore the many of children with learning problems were not being identified in the school system.

Unfortunately, the Medical Children's Centre Dallas, cohort was very heterogeneous including children with multiple etiologies leading to transplant. This included chronic liver disease, rapid fulminant failure, and patients with tumors and no underlying liver dysfunction. Therefore the pre-transplant factors that could potentially affect intellect varied substantially.

Wayman (1997) provided a much more homogeneous cohort of patients by examining only children with the diagnosis of biliary atresia. The findings of the

study demonstrated infants with a developmental quotient (DQ) less than 70. The DQ is similar to FSIQ in children < 3 ½ years of age. The study also stated that up to 60% of the infants were classified as delayed or borderline delayed. This study utilized a definition of borderline delay, of a score < 90 as borderline. It is important to note that this study examined children at an earlier point post-transplant, at 6 and 12 months post-transplantation compared to others that only examined patients at least two years post-transplant (Krull 2002, Kennard 1999, Schultz 2003).

Except for Wayman's study, all other studies had very heterogeneous patient populations pre-transplantation (Zitelli 1988, Stewart 1989, Kennard 1999, Gritti 2000, Adebeck 2003, Schultz 2003, Krull 2003). Despite the heterogeneity all cohorts demonstrated a DQ/FSIQ less than the expected population normative mean of 100 $\pm$ 15, with the study mean results ranging from 85-94. All the studies also demonstrated a prevalence of delay, DQ/FSIQ < 70, far in excess of the normal population. Normative population results predict that approximately 2.27% of the population will have a DQ/FSIQ < 70 (delayed). All the studies that provided information about the prevalence of delay demonstrated rates in excess of the predicted, with studies results ranging from 5% to 24% delayed.

More recent studies have examined emotional/psychological well-being and its association with cognitive outcomes (Adeback 2003, Gritti 2001). Again these studies demonstrated below normative full scale score IQ (FSIQ), Adeback's cohort demonstrated a mean of 86.6 and Gritti's cohort was 91.6. As well as impaired emotional/psychological function, Adeback's cohort analysis demonstrated an

association between poorer cognitive function with subnormal emotional development.

Others have compared children with liver transplantation to children with other chronic illnesses, most notably cystic fibrosis (Krull 2003). This was done in an attempt to control for early onset disease, nutritional and growth impairment. Their small cohort demonstrated that children post-transplantation have a lower FSIQ and that their most impaired domain is in the area of receptive language.

Unfortunately across all studies there was not an inter-study consistency in respect to specific areas of deficit. For example, some studies demonstrated verbal IQ deficits (Krull 2003, Wayman 1997) and others non-verbal IQ deficits (Schultz 2003, Kennard 1999, Stewart 1991). Many of the studies have attempted to analyze for predictive variables for developmental/cognitive delay. Nutritional status pre-transplant has been demonstrated to be predictive in some studies but not in others (Wayman 1997, Schultz 2003). Biochemical markers of severity of liver disease have been predictive in other studies. (Krull 2002, Wayman 1997) These inconsistent findings of specific delays and predictive variables may have been influenced by the heterogeneity of the cohorts and their relatively small sizes, ranging from 15 to 50 participants.

It is important to note that all previous studies have demonstrated developmental/cognitive delay and that this observation is an important outcome post-transplant. Unfortunately, because of the small number of children assessed and the variable findings there has not been an ability to develop a targeted approach to

change clinical transplant management. The methodological deficiencies of the previous studies and the importance of this functional outcome highlight the need for further research into this area.

Table 2.1 Summary of studies examining the developmental/cognitive delay associated with childhood liver transplantation.

Author **Publication Date**	**Study Subjects** **Demographics**	**Follow-up**	**Measurement**	**Statistical Analysis**	**Results:** **Cognitive testing and variables predictive of cognitive results**
Zitelli* # 1988	Eligible: 65 Participated: 29 Demographics: Unknown	Follow-up period: 2-7 years	BSID Stanford Binet LM WISC-R	t-test and Wilcoxon matched pair signed rank to compare FSIQ pre and post-OLT	Mean FSIQ: 93.3 PIQ: Unknown VIQ: Unknown Specific deficits: Unknown Predictive variables: Unknown
Stewart* # 1989	Eligible 37 children Participated 29 (78%) Participants: 18 female, 11 male	Follow-up period: 1 year post-transplant	BSID Stanford-Binet WISC-III	Wilcoxon matched pairs test to compare mental, motor, social function and growth pre and post-OLT Pearson correlation on role of steroid dose and growth, FSIQ as	FSIQ mean: 94 DQ mean: 84 PIQ mean: 95 VIQ mean: 93

Author Publication Date	Study Subjects Demographics	Follow-up	Measurement	Statistical Analysis	Results: Cognitive testing and variables predictive of cognitive results
Stewart 1989	Age range: 20 months – 16 years Mean age: 6 years			dependent variable Mann-Whitney test for difference between groups and their cognitive function	FSIQ < 70: 7/29 (24% Specific deficits: nonverbal intelligence, visiospacial deficits, decreased abstraction and concept formation Predictive variable: Unknown
Wayman 1997	Eligible: 59 Participated: 40 (68%) Participants: Term infants with biliary atresia transplanted < 2 years of age 25 female, 15 male Age range: 17 to 23	Follow-up period: Assessed 6 and 12 months post-OLT	BSID-II	ANOVA for parametric and Fisher Exact for nonparametric measures analyzing disease and transplant variables association with neurodevelopmental outcome.	DQ mean: 92 DQ < 70: 2/40 (5%) Specific deficits: expressive language delay Predictive variables: low albumen, weight < 5%

Author Publication Date	Study Subjects Demographics	Follow-up	Measurement	Statistical Analysis	Results: Cognitive testing and variables predictive of cognitive results
	months Mean age: 21 months				
Kennard [*#] 1999	Eligible: Unknown Participated: 50 Participants: 23 female, 27 male Age range: 6 – 23 years Mean age: 11 years	Follow-up period: 3 – 9 years	WPSII-R WISC-III Stanford Binet	Paired t-test: to compare IQ pre and post-OLT Chi-square: cognitive outcomes for biliary atresia versus other diagnoses ANOVA: comparing the three cognitive groups (delayed, learning disabled and normal) between group differences with clinical variables	FSIQ mean: 85 DQ mean: 86 PIQ mean: 87 VIQ mean: 86 FSIQ < 70: 9/50 (18%) Specific deficit: visiospatial defects (math, written language) Predictive variable: none found

Author **Publication Date**	**Study Subjects** **Demographics**	**Follow-up**	**Measurement**	**Statistical Analysis**	**Results:** **Cognitive testing and variables predictive of cognitive results**
Schultz [*#] 2003	Eligible: 39 patients Participated: 29 (74%) Participants: 15 female, 14 male Age range: 6 – 12.5 years Mean age: 8.4 years	Follow-up period: 3 – 10 years Mean follow-up: 6.4 years	Kaufman ABC	Assessing differences of cognitive testing between groups: t-test Assessing association between cognitive results and clinical variables: Multiple regression	FSIQ mean: 93 FSIQ < 70: Unknown Specific deficits: sequential processing scale Predictive variable: height at transplant
Adeback [*#] 2003	Eligible: Unknown Participated: 21 Participants: 9 female, 12 male Age range: 4 – 17 years Mean age: 9.6 years	Follow-up period: Unknown	WPPSI-R WISC-III	Unknown	FSIQ mean: 86.6 PIQ mean: 84.5 VIQ mean: 90.6 FSIQ < 70: 3/20 (15%) Deficits: Unknown Variables: Unknown

Author Publication Date	Study Subjects Demographics	Follow-up	Measurement	Statistical Analysis	Results: Cognitive testing and variables predictive of cognitive results
Krull 2003	Eligible: 42 Participated: 15 (36%) Participants: 11 female, 4 male Age range: 4-17 years Mean age: 9.6 years	Follow-up period: Unknown	WPPSI-R WISC-III	Unknown	FSIQ mean: 90 PIQ mean: 96 VIQ mean: 86 FSIQ < 70: 2/15 (12%) Specific deficits: delayed language Predictive variables: high bilirubin, # hospitalization first year post-OLT

• includes patients with no chronic liver disease (tumor, in-born error of metabolism)

includes patients with chronic liver disease and/or transplant at > 6 years of age

BSID-II:	Bayley Scales of Infant Development-Second edition
WPPSI-R:	Wechsler preschool and Primary Scales of Intelligence-Revised
WISC-III:	Wechsler Intelligence Scale for Children-Third edition
DQ:	Developmental quotient
FSIQ:	Full scale score intelligence quotient
PIQ:	Performance intelligence quotient
VIQ:	Verbal intelligence quotient
FSIQ < 70:	Clinical definition of cognitive delay

2.1.2

The search strategy for pediatric post-liver transplant HRQOL yielded 306 citations, fifteen papers were reviewed, after screening of abstracts, 5 papers fulfilled all of the inclusion criteria (Alonso 2003, Bucavalus 2003, Schultz 2003, Midgley 2000, Apajasalo 1997). The inclusion criteria were: i) that the papers had to be pediatric post-liver transplant cohorts. Apojasalo (1997) included renal, heart and liver recipients but did separate some of the data on the liver recipients, therefore the paper was included; ii) all references had to have utilized a validated pediatric HRQOL instrument. Papers that utilized surrogate markers describing HRQOL, i.e. number of hospital readmission, attendance in school, engaged in sports, were not utilized. Schultz states that they utilized a validated pediatric measure, in German. Although the authors failed to name the questionnaire the paper was still included. A summary of the eligible papers is presented in table 2.2. This includes the patient demographics, follow-up period, measurement administered, type of statistical analysis and results of the HRQOL testing.

There is one disease specific questionnaire for adult HRQOL post-liver transplant: the NIDDK-LTD Quality of Life (QOL). This instrument was constructed by experts in liver transplant/hepatology (Tarter 1998). To date, this instrument has not been validated. There is no disease specific HRQOL instrument for Pediatric liver transplant.

The pediatric transplant HRQOL literature is less well developed. Many papers from the early 1990's attempted to measure HRQOL in a surrogate or non-

standardized method. Some papers state there is an improved HRQOL post-pediatric transplant because the children are back in school, appear happy, participate in extra-curricular activities and their parents' marriage has remained intact (Sokol 1994, Stone 1997). Others have constructed their own non-validated questionnaire.(Asonum 1999) These are important functional outcomes but they lack standardization and objectivity.

Generic pediatric HRQOL instruments have been studied in the pediatric liver transplant population. The Health Utilities Index II (HUI-2) was administered by Midgley et al to 51 children post-liver transplant (Midgley 2000). This measure constructs a utility score from a multi-attribute health status questionnaire (MAHS). The focus of the HUI is on the core attributes of health status. The results were compared to a sample of school age children from Hamilton-Wentworth region, Ontario. Functional limitations were present in 90% of transplanted children versus 50% in the reference population. The most commonly affected domains were emotion and pain. The children post-transplant demonstrated a utility score of 0.86 compared to a reference population score of 0.95 (Midgley 2000).

Alonso (2003) was concerned that the HUI-II was not sensitive enough to detect differences among members of the pediatric liver transplant population and the domains of self-esteem, social function and family dynamics were not adequately explored. Therefore they administered the Child Health Questionnaire-Parent Form 50 (CHQ-50), which incorporates the domains of physical health, emotional functioning, social functioning, school functioning and psychosocial health, to a group of 86 children, 5-18 years who were at least 2 years post-transplant. Overall

they had a reasonable quality of life. The sub-scale scores most diminished included global health perceptions and emotional impact on parents and family activities.(Alonso 2003) Interestingly, transplant families describe better family cohesion compared to the general population. Alonso's study was noted to have bias because it was a mail out survey and there was a significant difference between the respondents and non-respondents by ethnicity and socioeconomic status. Bucuvalus (2003) attempted to correct for this by administering the questionnaire during clinical visits. The authors utilized both the CHQ-50 and the Pediatric Quality of Life 4.0 (Peds QL 4.0). The results of the CHQ-50 demonstrated the physical and psychosocial functions were the most affected post-transplant. The Peds QL 4.0 results appeared to be more sensitive to change with diminished scores across all domains. These lower scores were similar to results of children with other chronic illness. Unlike Alonso's study, Bucuvalas was able to demonstrate predictive variables for higher HRQOL scores, they found that age at transplant (younger) and maternal education, were predictive of a better HRQOL outcome.

In contrast to Bucuvalus, Schultz published a paper in 2003 which demonstrated that social and physical function domains were preserved post-liver transplant but psychological domains were lower than expected. Unfortunately, Schultz states that they utilized a validated HRQOL measure but does not name the measure in the publication.

Apajasalo et al examined HRQOL in children with different types of solid organ transplants (Apajasalo 1997). Unfortunately the liver transplant patients comprise only a small fraction of the children studied. The instruments utilized were

the 16D for 12-15 year olds and the 17D for 8 to 11 year olds. The children with early onset of disease and closer temporal proximity to their transplant exhibited the greatest burden on their health status.

Pediatric literature examining HRQOL post-liver transplant is very sparse despite quality of life being one of the many indications for transplantation. The studies have demonstrated impaired HRQOL compared to population based studies and HRQOL comparable to other pediatric chronic disease groups (Alonso 2003). The previous studies had methodological issues including the utilization of very heterogeneous cohorts. These issues demonstrate the requirement for further analysis of the HRQOL as it is an important outcome post-transplant. The requirement is for both descriptive and predictive assessment of diminished HRQOL post-liver transplant.

Table 2.2 Summary of studies examining pediatric HRQOL post-liver transplantation

Author **Publication date**	**Study Subjects Demographics**	**Follow-up Period**	**HRQOL Measure**	**Statistical** **Analysis**	**Results**
Apajasalo 1997	Participants: Unknown for liver transplant patients	Unknown for liver transplant	Multi-dimensional questionnaire15 D, 16D or 17D	Unknown	Scores similar to controls for pre-adolescents 0.92 versus 0.937 (only results for liver recipients)
Midgley 2000	Eligible: 73 Participated: 51 Participants: 3-18 years of age Mean age: 4.94 years.	Follow-up period: 2 years post-transplant	HUI-II	Unknown	Emotion and pain most affected attributes 22% had limitations in cognition Mean utility score 0.86; reference population score 0.95 ($P< 0.05$)
Bucuvulas 2003	Eligible: 85 Participated: 77	Follow-up period: > 6 months post-transplant	CHQ-50 PedsQL 4.0	t-test: to compare the mean score with published mean scores for the CHQ-	Lower physical health, emotional functioning, social functioning, school functioning and psychosocial

Author Publication date	Study Subjects Demographics	Follow-up Period	HRQOL Measure	Statistical Analysis	Results
Bucuvulas 2003	Participants: 46 female, 31 male 5 – 18 years of age	Mean follow-up: 5.8 years		50 and PedsQL 4.0 Stepwise multiple regression: between summary scores and demographic and practice variables assessing for predictive variables	health. Similar summary scores to other chronic diseases Predictive variables: age at transplant, time since transplant, recent hospitalizations, maternal education and race were predictors of physical health scores
Alonso 2003	Eligible: 86 Participated: 55 Participants: 30 female, 25 male 5 – 18 years of age Mean age: 9.5 years	Follow-up period: 2-years post-transplant Mean follow-up: 6 years	Child Health Questionnaire 50 (CHQ-50)	t-test: comparing transplant patients' summary score versus other patients' with chronic illness Pearson correlation: assessing correlation between summary	Lower physical function domain Increased emotional stress and disruption of family activities Predictive variables: None

Author Publication date	Study Subjects Demographics	Follow-up Period	HRQOL Measure	Statistical Analysis	Results
Alonso 2003				scores and practice variables Step-wise multiple regression: between subscale and summary scores and potential predictive practice variables.	
Schultz 2003	Eligible: 39 Participated: 29 Participants: 15 female, 14 male 6 – 18 years of age > 3 years post transplant	Follow-up period: > 3 years post-transplant Mean follow-up: 6.4 years	Unknown	T-tests: assessing the difference between parental and patient summary scores	Low average everyday functions Normal social and physical function

Chapter 3

Objectives

3.1 General Research Objectives

The purpose of this study was to characterize the developmental/cognitive and health-related quality of life outcomes in a cohort of children post-liver transplant. There has been very little published on these outcomes and previous studies have had methodological issues that may have prevented their ability to demonstrate patterns or identify clinical practice variables that would allow for targeted intervention or change of practice. The aim of this study was to assess a homogeneous population of children, in a further attempt to delineate the potential clinical practice variables that may be modified to improve the functional outcomes of cognitive/developmental and health-related quality of life.

Another objective was to provide individual cognitive testing results to the families of transplanted patients to support them to access full preschool or school educational assistance if required. This information is not reportable due to patient confidentiality.

3.2 Specific Research Objectives:

1. To assess the developmental, cognitive and school related performance of a cohort of children with infantile onset chronic liver disease who were transplanted in their preschool years at the University of Alberta from 1990-2001.

2. To assess the modifiable and non-modifiable variables that may be contributing to developmental/cognitive delay in these children.

3. To assess health related quality of life in a subset of patients who were greater than 3 years of age at the time of assessment and received all their follow-up care at the University of Alberta. These results will then be compared with the results of a published reference cohort.

4. To assess the modifiable and non-modifiable variables that may be contributing to the decreased quality of life in this cohort of post-liver transplant patients.

Chapter 4

Objectives 1 & 2

Methods, Results, Discussion

4.1 Methods

This study details the developmental, cognitive and school performance outcomes in a cohort of children with infantile onset liver disease, who were transplanted at less than or equal to 6-years of age. The study also attempted to identify modifiable and non-modifiable practice variables that may contribute to the developmental and cognitive delay.

4.1.1 Subjects

This study recruited children with the following criteria: 1) children were from Western Canada, who were transplanted at the University of Alberta Hospital between January 1990 to December 2001; 2) infantile onset of end-stage liver disease; 3) liver transplantation $\leq$ 6 years; 4) at least 6 months post-liver transplant; 5) continue to be followed at the University of Alberta or designated referral sites.

Patients were excluded if they had fulminant liver failure, tumour, or another disorder that may contribute to developmental/cognitive delay, for example an inborn error of metabolism such as a urea cycle defect. All patients underwent a detailed neurological exam by a pediatric neurodevelopmental specialist and had audiology testing to exclude other causes of poor test results.

Immunosuppression management of these patients was accepted standard therapy. From 1990-1996 this included cyclosporin A, azothioprine and prednisone and the protocol was changed to tacrolimus and prednisone, from 1997 to 2001

Families/patients were contacted prior to their annual liver transplant follow-up or were registered during the immediate post-transplant course for follow-up at one year. The testing was performed in the Neonatal and Child Follow-up Clinic, at their referring sites. These clinics have extensive experience in clinical and research assessments of developmental, cognitive and school-related performance.

4.1.2 Predictive Variables

Predictive variables that may be contributing to developmental/cognitive delay were selected based on suggestions from previous literature (Stewart 1989, Stewart 1994, Wayman 1997, Krull 2003) and clinical hypotheses. These variables were divided into pre-transplant, peri-operative and post-transplant. Data for these variables was obtained from charts and the clinical database of the University of Alberta Hospital's liver transplant program. Pre-transplant variables included, age at transplant, transplant disease severity status at time of transplant, etiology of liver disease, height and weight percentiles, serum albumin, serum ammonia, gender, socioeconomic status and number of hospitalizations pre-transplant. Peri-operative variables were major surgical complications and early re-transplantation. Post-transplant variables included number of days of elevated calcineurin inhibitors (defined as a cyclosporin level greater than 450 μgm/l or a tacrolimus level greater than 15 μgm/l), number of significant infections and number of episodes of rejection.

Predictive variables for the participating children and those who were lost to follow-up or died are presented in tables 4.2 and 4.3. Due to the incomplete records only pre-transplant variables are available for those patients who were not followed up.

4.1.3 Measurement

Standardized Testing

The assessment of developmental and cognitive status was conducted utilizing age appropriate standardized testing. Three measures were administered either the Bayley Scales of Infant Development-II (BSID-II), the Wechsler Preschool and Primary Scales of Intelligence-R (WPSSI-R) or the Wechsler Intelligence Scales for Children-III (WISC-III). These widely used measures have broad applicability to general and specific special needs group populations. All scores are based on population normative data with a mean of 100 and a standard deviation of 15. The choice of cognitive/developmental measures is based upon the age of the child, the BSID-II for infants and toddlers, the WPSSI-R for preschool children and the WISC-III for school age children (table 4.1).

All testing was administered in a similar fashion during a one-on-one encounter between the child and an early childhood psychologist or an educational psychologist, depending on the age of the child and the testing performed. Parents were present for the BSID-II and the child was either beside or on the parent's lap during the testing. Parents of the child older than 3 ½ years are not present during the testing.

Each standardized measure consists of several subsections. The child was administered a battery of questions/tasks. The standard of difficulty of the entry questions/tasks was at or below the expected capability of the child. The child then advanced through the questions/tasks until they could no longer formulate a specific number of correct responses (this varies with each subsection). Then the child would

have reached their maximum performance in that area. This performance was then awarded a raw score. Raw scores were then tabulated and converted into standardized scores. Delay is defined as a score < 70, although children with a score < 85 will require a modified learning environment. Therefore we functionally classified these patients as borderline delayed (FSIQ 84-70).

All of the above mentioned instruments are widely used for assessing developmental and cognitive function. Their purpose, reliability and validity have been well established and published and is summarized in appendix B.

In addition to cognitive testing, children greater than 6 years had assessment to acquire more information about their learning profile and school performance. This supplemental information was obtained using the Wechsler Individual Achievement Test (WIAT) for school performance. The WIAT represents a composite of the typical curricular specifications in reading, mathematics and language arts. The definition of delay (also referred to with this measurement as learning disability) differs from cognitive testing with a score less than 85 defining delay in that specific learning domain. So the WIAT provides complementary information about the cognitive/learning patterns of children.

The Beery test of geometric design is a rapid screening tool for visual motor integration and represents aspects of performance intelligence and was administered to the children who underwent Wechsler cognitive testing (WPSSI-R, WISC-III).

The Vineland Adaptive Behavioral Scales (VABS) allows for assessment of adaptive behavior and social function. It is conducted in a semi-structured interview format. It

can be administered to all the children in the study as there are normative scores for all included age groups. It is often used to complement intelligence scales as it measures social competence which is not included in the developmental (BSID-II) and cognitive measures (WPSSI-R, WISC-III).

Table 4.1 Summary of the applicable age ranges, subtesting and standardized information for standardized measures.

Indication	Measure	Result
Developmental testing ages 2 months to 3 ½ years	Bayley Scales of Infant Development –II (BSID-II)	Mental developmental index (MDI=DQ), motor score (PDI)
Cognitive testing 4 to 6 years	Wechsler Primary Preschool Scales-Revised (WPPSI-R)	Full scale score IQ (FSIQ) Performance IQ (PIQ) Verbal IQ (VIQ)
Cognitive testing 6 to 17 years	Wechsler Intelligence Scale for Children –III (WISC-III)	Full scale score IQ (FSIQ) Performance IQ (PIQ) Verbal IQ (VIQ)
School related performance	Wechsler Individual Achievement Test (WIAT)	Subject specific scales
Visual motor integration	Beery	
Adaptive behavior function (social and daily living)	Vineland Adaptive Behavioral Scales (VABS)	Communication score Daily living score Socialization score Motor score Composite score

4.1.4 Ethics

Ethics approval for patient contact and evaluation was obtained from the Health Research Ethics Board, University of Alberta.

Primary care providers had the study explained during a telephone interview conducted by a research nurse. Preliminary consent was obtained at that time and arrangements were made for the evaluation. Formal written consent and further explanation of the study was provided at the time of developmental/cognitive evaluation.

4.1.5 Statistical Analysis

Statistical analysis was performed with SPSS 12.0. All results of developmental/cognitive function, including DQ, FSIQ, PIQ, VIQ, VABS, WIAT and Beery; and the predictive variables were analyzed assessing the mean, standard deviation (SD) and range. This provided a description of the cohort. Student's t-test and Chi-square analysis were utilized to assess differences between different subsets of the cohort. ANOVA was performed to assess the three groups of patients with respect to predictive variables, participating patients, the patients who died and those lost to follow-up.

Regression and correlation analysis were performed with the DQ/FSIQ, FSIQ, PIQ, VIQ, and Beery scores as the continuous dependent variable with the continuous pre-, peri-and post-transplant practice variables; age at transplant, socioeconomic status, as measured by the Blishen Index, height percentile, weight percentile, serum albumin, serum ammonia, number of days of elevated calcineurin inhibitor(CI), number of significant infections, number of surgical complications, number

of episodes of rejection, as independent variables. Predictive variables were included in the final multivariate analysis if the univariate analysis demonstrated a $p < 0.2$. Only variables or combination of variables with a p value of ≤ 0.05 are reported in the final multivariate model. The predictive practice variables of gender and diagnosis were dichotomous and were analyzed with student's t-test analysis.

4.2 Results

4.2.1 Subjects

During this period 74 transplants were performed on 64 children and 42 of these patients were potentially eligible at time of transplant. There were 5 deaths < 6 months post-transplant. Seven patients did not participate, 5 because they were no longer followed on-site or at a Western Canadian referral site and 2 families refused participation. Of the patients who met all the eligibility requirements, 30/37, 81% participated and of the patients still in region or referral region 30/32, 94% participated.

The majority of patients followed had the underlying diagnosis of extra hepatic biliary atresia (EHBA) (21/30). The other diagnoses included three children with α 1-antitrypsin deficiency, three with neonatal hepatitis and two with Alagille's syndrome. The minority of patients biliary atresia may have a biliary system that is amenable to a palliative procedure, a Kasai portoenterostomy, which significantly delays and occasionally removes the need for liver transplant. A small comparison group of four children, with a functioning Kasai portoenterostomy were assessed to see if their developmental/cognitive outcome differed from those children with biliary atresia and a liver transplant.

Patient characteristics are presented in table 4.2 and 4.3. Characteristics of the patients who died or were lost to follow-up are presented in table 4.3. The only significant difference between the children who died or were lost to follow-up and those who participated is gender ($p = .048$) with a higher proportion of males in the lost to follow-up group. There was no difference in any pre-transplant variables between those

who were followed and those who died or were lost to follow-up. There was a difference in the number of hospitalizations between those who participated and the five children who died ($p < .05$, Scheffe post hoc analysis of ANOVA) (Table 4.3). The children who died had fewer pretransplant hospitalizations.

Table 4.2 Descriptive characteristics of study participants (n=30)

Gender	20 females; 10 males
SES (Blishen 1987)	42 (Range: 21-76)
(Canadian mean 43)	
Etiology	21 biliary atresia, 9 other
Median age at transplant	1 year 5 months (Range: 3 months – 6 years)
Status at transplant	21 at home; 9 hospitalized
Mean time elapsed since transplant	3 years 2 months (Range: 6 months – 12 years)

Table 4.3: Descriptive pre-transplant variables of 30 assessed and 12 not assessed children after liver transplant at ≤6 years of age: n(%), mean ± SD

Pre-transplant variables	Assessment status of children					
	total	assessed	Lost	death		
	n = 42	n = 30	n = 7	n = 5	ANOVA or Chi-square analysis	p*
gender: male	19 (45%)	10 (33%)	5 (71%)†	4 (80%)†	6.11*	0.05
socioeconomic status	41 ± 16	42 ± 17	47 ± 16	35 ± 13	0.79	.46
height: <5th %ile	17 (40%)	9 (30%)	5 (71%)	3 (60%)	4.94	.31
weight: <5th %ile	6 (38%)	8 (27%)	5 (71%)	3 (60%)	5.97	.29
diagnosis: biliary atresia	31 (74%)	21 (70%)	6 (86%)	4 (80%)	0.84*	.66
# hospitalizations	1.9 ± 1.6	2.3 ± 1.6	1.3 ± 1.5	0.4 ± 0.9†	4.31	0.02
serum albumin g/L: lowest	30 ± 8	29 ± 9	29 ± 5	33 ± 4	0.61	.55
serum ammonia umol/L: highest	45 ± 48	49 ± 55	40 ± 22	28 ± 18	0.42	.66
age at transplant: years	2.1 ± 1.7	2.2 ± 1.8	1.8 ± 1.9	1.6 ± 0.7	0.32	.73

* Chi-square

† denotes difference from those assessed

Table 4.4: Pre- and post-transplant variables for 30 assessed younger (BSID-II and older (WPSSI-R, WISC-III)children after liver transplantation at ≤6 years of age: n (%), mean ± SD.

Variables	Total	Assessment Age (months)		t-statistic or chi-square*	p
		<42	>47		
	n = 30	n = 10	n = 20		
Pre-transplant					
gender male	10 (33%)	5 (50%)	5 (25%)	1.88*	0.17
socioeconomic status	42 ± 17	43 ± 14	41 ± 19	0.20	0.82
height % ile	21 ± 28	28 ± 35	18 ± 23	0.28	0.79
weight % ile	22 ± 28	21 ± 27	22 ± 29	-0.48	0.64
diagnosis: biliary atresia	21 (70%)	6 (60%)	15 (75%)	0.43*	0.52
# hospitalizations	2.3 ± 1.6	1.7 ± 1.1	2.7 ± 1.7	-1.59	0.12
serum albumin g/L: lowest	29 ± 9	26 ± 8	31 ± 9	0.97	0.32
serum ammonia umol/L: highest	49 ± 55	59 ± 77	43 ± 42	-1.49	0.15
Post-transplant					
# infections	3.4 ± 3.7	3.2 ± 3.1	3.1 ± 4.0	-0.90	0.38
# surgical complications	0.8 ± 1.2	1.1 ± 1.6	0.6 ± 0.9	-1.20	0.24
# episodes of elevated calcineurin inhibitor	8 ± 6.5	9.5 ± 7.7	7.2 ±5.8	0.08	0.94
# rejections	1.4 ± 1.6	1.4 ± 1.2	1.4 ± 1.8	-1.7	0.10

As noted from tables 4.2-4.4 the assessed cohort is mostly between one to two years of age (15/30)at the time of transplant. They have an average socioeconomic status, with the Canadian mean 43, (Blishen 1987). Although the mean height and weight are at the 20 percentile, the median height and weight are at or below the 5 percentile (15/30). Serum ammonia levels were slightly elevated (48 μmol/l ± 55) and a serum albumin was low pretransplant (29g/L ± 8.6). Most patients were hospitalized at least twice prior to transplant (2.3 ± 1.5). Postoperatively most patients experienced episodes of rejection (1.4 ± 1.6), elevated calcineurin inhibitors (8 ± 6.5) and episodes of infection (3.4 ± 3.7), with relatively few having surgical complications (.77 ± 1.2). Most of these post-transplant surgeries were for re-transplantation for early thrombotic events (6/30).

4.2.2 Developmental/Cognitive Testing Results

Due to the age range of the participants, ten children (< 42 months of age) were administered the BSID-II and twenty children (> 47 months of age) had Wechsler testing (WPPSI-R, WISC-III) and Beery. The twenty older children have more extensive results, including a DQ/FSIQ, a performance IQ (PIQ), verbal IQ (VIQ) and Beery (visual motor integration). This additional information provides information on different aspects of cognitive function of both performance and verbal function.

A comparison of the younger (n = 10) and older (n = 20) was performed with student's t-test and Chi-square to assess for any difference between the two groups. There were no significant differences between the groups in development/cognitive test scores, VABS (composite and subsections) score and all practice variables (table 4.5).

The mean DQ score (n=10) was 75 and the mean FSIQ was 84. The results of the collapsed DQ/FSIQ was 81 ± 17. The range of scores varied from the lowest possible score of 49 to a high score of 121. Population normal values are 100 ± 15, with 70 being delayed (the clinical definition of mental retardation) and 70-84 borderline delayed.

Examining specific aspects of cognitive/brain function, reveals that the mean PIQ was 86 ± 19 and the VIQ 84 ± 13. Visual motor integration as screened with the Beery had a mean of 82 ± 12. Cognitive testing provides performance subscores and verbal subscores. We evaluated the results to see if there was a specific pattern of deficit, i.e. performance versus verbal scores. There was no pattern noted with 9/20 children having a higher performance score and 11/20 a higher verbal score. These two groups (higher performance IQ, higher verbal IQ) were then compared in regards to any significant

differences in practice variables. The only significant difference was that children who had a higher PIQ had more hospitalizations (2.93 versus 1.73; $p = 0.035$).

Table 4.5: Psychological Test Results for 30 assessed younger and older children after liver transplantation at ≤6 years of age: mean ± SD.

	Assessment Age (months)			
	<42	>47		
Outcome Variable	n = 10	n = 20	t-test	p
Developmental Quotient/ Intelligence Quotient	75 ± 20	84 ± 15	-1.35	0.19
Performance Intelligence Quotient	na	86 ± 19		
Verbal Intelligence Quotient	na	84 ± 13		
Vineland Adaptive Behaviour Scales				
communication	85 ± 18	90 ± 17	-0.84	0.42
daily living	85 ± 15	94 ± 15	-1.60	0.12
socialization	99 ± 20	104 ± 12	-0.89	0.38
motor	85 ± 19	98 ± 18	-1.83	0.08
composite	85 ± 17	93 ± 17	-1.142	0.26
Visual Motor Integration	na	82 ± 12		

Note: reference means = 100 ± 15 (Bayley 1993, Wechsler 1976, 1981)

4.2.3 Comparative Populations

Four patients with biliary atresia and a functioning Kasai portoenterostomy had a mean DQ/FSIQ of 102 (scores 123, 113, 101, 75). This compares with the mean of the transplant cohort of 80.9, suggesting that delay is not due to the underlying diagnosis but rather chronic liver disease and liver transplantation.

Population normative data reveals that 14% of the population has a DQ/FSIQ between 84-70 and only 2.27% with a score < 70. This compares with our cohort which demonstrates 27% (8/30) DQ/FSIQ 84-70 and 27% (8/30) DQ/FSIQ < 70.

Patients from the initial generation, 1990-1996, of immunosuppression (cyclosporin A azothioprine/prednisone) had a mean DQ/FSIQ of 77. The mean DQ/IQ of the more recent immunosuppression (tacrolimus/prednisone) was 83.

Test/retest of five randomly selected patients demonstrated stability of the cognitive results over time. Patients were re-administered the WPSSI-R or WISC-III at a second time assessment at least one year after the first cognitive assessment. FSIQ results from the time one to time two assessment did not demonstrate any significant difference ($p=0.091$ Wilcoxon sign rank test).

4.2.4 WIAT (Subject Specific Testing)

Nine children were an appropriate age and developmental status to complete subject specific testing with the WIAT. The subject scores, standard deviations and score ranges are displayed in table 4.6. Learning disability in a subject is defined by a score less than 85. Learning delay may be further defined for the individual patient as a

difference of the subject specific score and the FSIQ, with the subject score ≥15 points lower than the FSIQ. Conversely, exceeding expectations is a subject score ≥ 15 points greater that the FSIQ. This subset of patients demonstrated specific patterns of deficit. Mathematics scores were poor. mean = 74 ± 13, with only one patient with a composite math score greater than 85 and three patients functioning ≥ 15 points below their FSIQ. Numeric operations demonstrated the greatest impairment, mean = 74 ± 10. Compared with the FSIQ, language skills tended to oûtperform expected with seven patients with a higher spelling score, six with a higher basic reading and five with a higher written expression.

Table 4.6: School achievement scores of 11 children after liver transplant at ≤6 years of age: mean ± SD, n (%)

Achievement	Score Mean ± SD	Number (%) of children with abnormal scores*(n=11)
Composite Reading	85 ± 18	3 (27%)
- basic reading	92 ± 16	2 (18%)
- reading comprehension	82 ± 15	6 (55%)
- listening comprehension	86 ± 16	8 (73%)
Composite Mathematics	74 ± 13	9 (82%)
- mathematics reasoning	80 ± 13	8 (73%)
- numeric operations	74 ± 10	6 (55%)
Spelling	91 ± 17	4 (36%)

* abnormal score is a standard score of <85.

4.2.5 Vineland Adaptive Behavioral Scales

VABS as reported by the primary care provider range from 88 to 102 (table 4.5). Socialization is the only totally preserved domain. The results of the VABS communication and composite scores differ from the DQ/FSIQ scores and did not demonstrate correlation (Pearson correlation VABS communication p = .07, VABS composite p = .371).

4.2.6 Predictive Variables

Univariate regression analyses of the dependent variables, DQ/IQ, FSIQ, VIQ, PIQ, and Beery with all pre- and post-transplant predictive variables were performed. Figures 4.1 and 4.2 are examples of the scatter diagrams demonstrating the linear relationship between the variable and dependent outcome. Variables with a p value of < 0.2 were included in the regression model. Potential predictive variables and their slope, standard error (SE), p value and R squared are presented in table 4.7. Student's t-test for the dependent variables and dichotomous predictive variables are demonstrated in tables 4.8, 4.9.

Predictive variables with a p value > 0.2 that were not used in the multiple regression model included:

- Beery: weight, albumin, number of days of elevated CI, Blishen Index, number of episodes of rejection
- DQ/FSIQ: age, albumin, number of days of elevated CI, number of infections, Blishen Index, serum ammonia, number of surgical complications, number of episodes of rejection

- FSIQ: age, weight, albumin, number of infections, Blishen Index, serum ammonia, number of surgical complications, number of episodes of rejection
- PIQ: age, weight, albumin, number of elevated days of CI, Blishen Index, number of episodes of rejection
- VIQ: age, height, albumin, number of infections, Blishen Index, ammonia, number of surgical complications, number of episodes of rejection.

Regression analysis examining variables predictive of developmental/cognitive delay (DQ/FSIQ), delay of PIQ, VIQ, Beery and VABS demonstrated some distinctive patterns. For the combined DQ/FSIQ, the diagnosis of biliary atresia was associated with a higher DQ/FSIQ and accounted for 14.7% of the variance (table 4.10). The subset of children who had Wechsler testing (n=20) found that almost 32% (table 4.10) of the variance was associated with the variables of height pre-transplant (a surrogate marker for nutritional status) and days of elevated calcineurin inhibitors. The interpretation is that short stature is associated with poorer cognitive function and more days of elevated serum calcineurin levels is also associated with decreased cognition. Note that the p value trends to significance, $p = .052$.

Verbal IQ results in the same 20 children also finds that 23% of the variance in their verbal score can be associated with elevated calcineurin inhibitors, with more toxic days associated with lower VIQ (table 4.10).

Performance function as evidenced by the PIQ and Beery demonstrates different predictors of impaired cognitive scores. The PIQ has 44.5% of its variance associated with pre-transplant height and serum ammonia. The correlation being lower height and

higher ammonia associated with lower PIQ. The Beery has the same predictors with 33% of variance due to the same variables with the same correlation (table 4.10).

Note that socioeconomic status is not a predictive variable for DQ/FSIQ, PIQ, VIQ, FSIQ, Beery or the VABS.

Figure 4.1 Sample scatter plot and regression lines for univariate analysis, Visual motor integration (Beery) and serum amonia. Slope = -.067; r squared .136

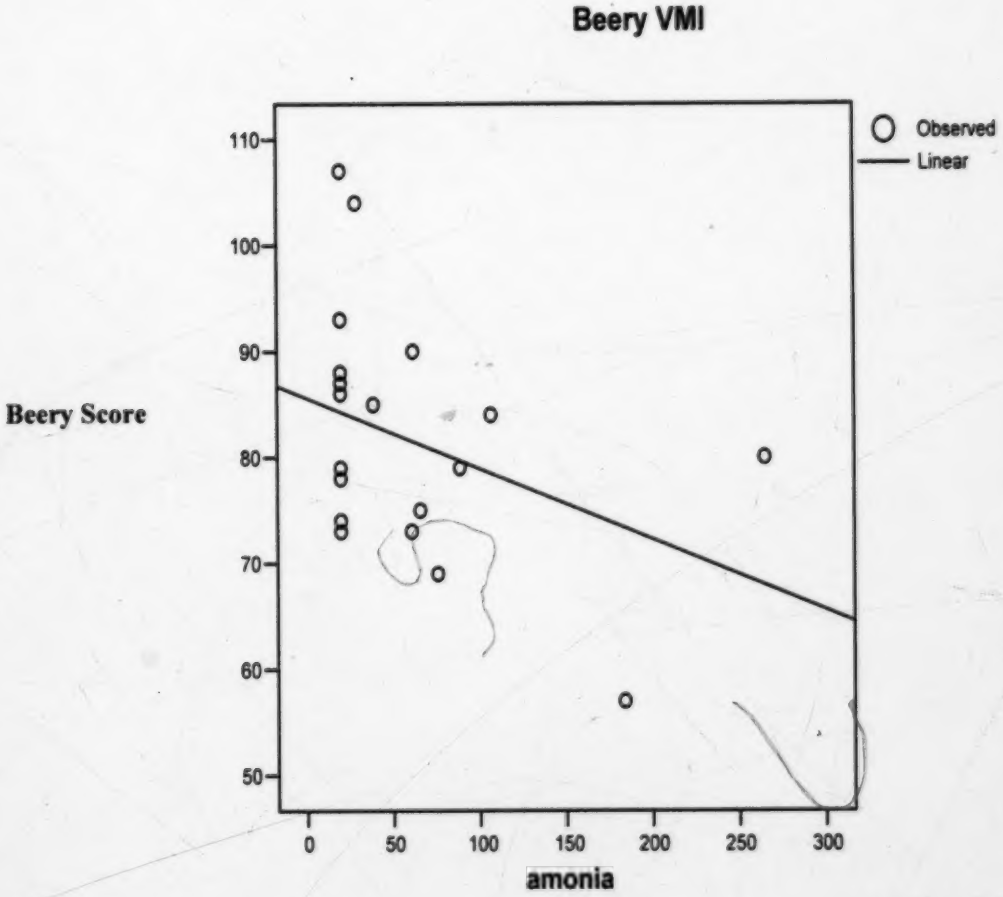

Figure 4.2 Sample of univariate analysis and regression line, Performance intelligence quotient and height percentile. Slope = .36; r squared = .198

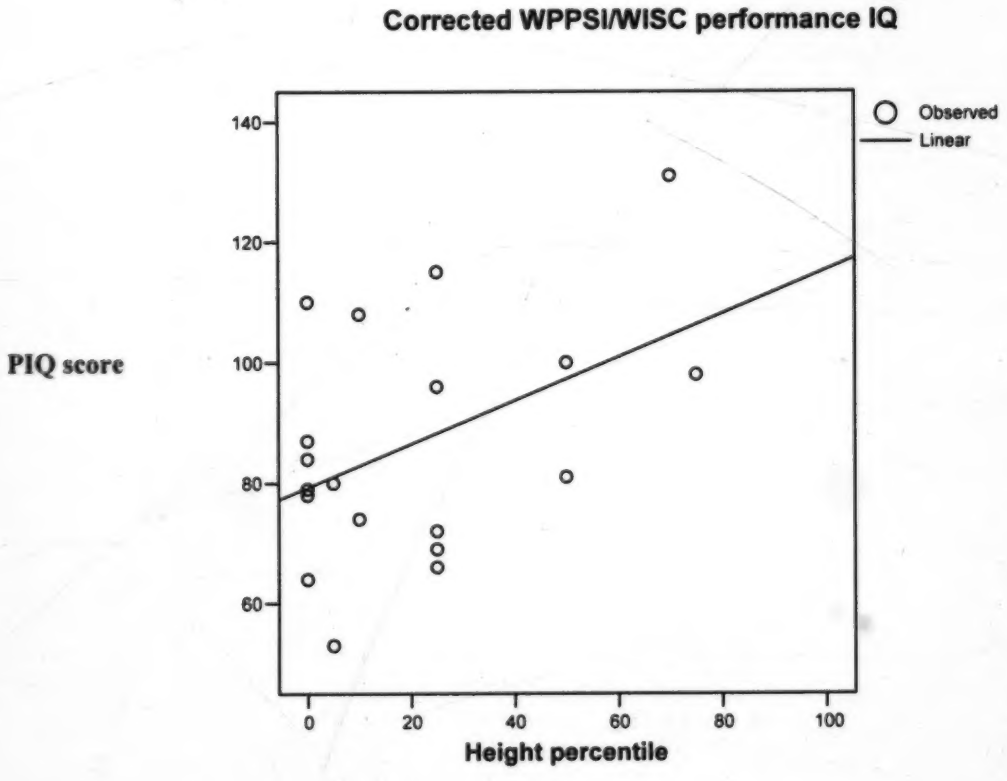

Table 4.7 Univariate regression analysis (variables with p <0.2)

Outcome Variable	Predictive Variable	Slope	Standard Error	P value	R^2
*DQ/FSIQ	Height percentile	0.197	0.112	0.088	0.100
	Weight percentile	0.153	0.112	0.184	0.062
FSIQ	Height percentile	0.245	0.141	0.098	0.144
	Number of days of elevated CI	-0.760	0.517	0.159	0.107
VIQ	Number of days of elevated CI	-0.968	0.417	0.032	0.231
PIQ	Height percentile	0.360	0.171	0.049	0.198
	Number of infections	-1.155	1.072	0.164	0.105
	Highest serum ammonia	-0.105	0.067	0.132	0.122
	Number of surgical Complications	-5.349	3.353	0.128	0.124
Beery	Age	-1.859	1.331	0.179	0.098
	Height percentile	0.155	0.109	0.171	0.101
	Number of infections	-1.049	0.633	0.115	0.132
	Highest serum ammonia	-0.067	0.040	0.110	0.136
	Number of surgical complications	-3.241	2.008	0.124	0.126

*DQ/FSIQ: Combined BSID-II and Wechsler FSIQ scores (n = 30)

Table 4.8 Dichotomous variables, t-test for gender and outcome variables

Outcome variable	Male	Female	P value
DQ/IQ	82.1 ± 13.5	80.3 ± 19.1	0.79
PIQ	95.2 ±14.6	83.5 ±20.3	0.255
VIQ	87.0 ±5.6	82.5 ± 15.1	0.527
FSIQ	89.8 ±7.2	81.9 ±17.1	0.333
Beery	85.4 ± 6.1	80.5 ± 12.9	0.426

Table 4.9 Dichotomous variables, t-test for diagnosis (Biliary atresia/other) and outcome variables

Outcome variable	Biliary atresia	Other	P value
DQ/IQ	85.1 ± 16.9	71.0 ± 14.2	0.036
PIQ	89.4 ± 21.4	77.6 ± 2.2	0.249
VIQ	84.7 ± 14.1	80.2 ± 11.8	0.527
FSIQ	86.1 ± 16.5	77.2 ± 10.0	0.278
Beery	82.3 ± 13.0	80.0 ± 7.1	0.717

Table 4.10 Multiple regression analysis for predictive variables and dependent outcomes

Outcome Variable	Predictive Variable	Slope	Standard Error	P value	R^2
*DQ/FSIQ	Biliary atresia	14.143	6.437	0.036	0.147
FSIQ	Height percentile	0.304	0.132	0.034	0.319
	Number of days of elevated CI	-0.993	0.476	0.052	
VIQ	Number of days of elevated CI	-0.968	0.417	0.032	0.231
PIQ	Height percentile	0.481	0.153	0.006	0.445
	Highest serum ammonia	-0.157	0.038	0.014	
Beery	Height percentile	0.224	0.101	0.039	0.332
	Highest serum ammonia	-0.091	0.038	0.027	

*DQ/FSIQ: Combined BSID-II and Wechsler scores (n = 30)

4.3 Discussion

Delay and borderline delay were quite frequent in this cohort of children, both in comparison to other reported transplant cohorts and the general population. The findings of 27% delayed and 27% borderline delayed with only 46% with normal intelligence is twice (borderline delayed) and fourteen times (delayed) the expected prevalence. Importantly there was no difference in clinical variables between the studied cohort versus those children who were lost to follow-up. Therefore the studied cohort appears to representative of all children transplanted at the University of Alberta. Developmental/cognitive impairment consistently affected all subsets of children, including; i) those who were younger at time of transplant and assessment versus the children who were older, ii) those transplanted more recently versus those who were transplanted during the first years of the transplant program.

Variables predictive of developmental/cognitive impairment were different for the different outcome measures. Regression analysis demonstrated clinical variables that were predictive of delay in the older children (n = 20) but did not demonstrate any predictive variables in the younger subset of children (n = 10). This was unexpected as there was no significant difference in the practice variables between the older and younger participants. This may be due to the under powering of the study with the small n = 10 in the younger group. In the older aged group, the FSIQ had 32% of its variance associated with growth failure and increased calcineurin inhibitor (CI) serum levels ($p = .052$). Combining the older and younger subgroups, the DQ/FSIQ did have the diagnosis variable predictive of developmental/cognitive outcome. The diagnosis of

biliary atresia was associated with a better DQ/FSIQ score. The fact that biliary atresia was associated with a better developmental/cognitive mental outcome may be attributed to the issue that other diagnoses may have associated congenital issues associated with a lower mental status. Alternatively, the natural history of biliary atresia is so well known resulting in these patients being transplanted at a different stage of end-stage liver failure.

The distinct cognitive domains of performance and verbal IQ demonstrated very different associated predictive variables. VIQ was associated with elevated calcineurin inhibitor levels compared to the PIQ and the Beery (visual motor integration) which had growth impairment and elevated serum ammonia levels as predictive variables.

The report of the primary care providers, as scored by the VABS, did not accurately reflect the results of the objective developmental/cognitive test results. The developmental/cognitive testing did not correlate with the cognitive sub-scores or composite score of the VABS. It is interesting to note that despite multiple hospitalizations and significant life threatening disease that the socialization domain is preserved in the VABS.

The subset of children who were able to complete school subject testing demonstrated learning disabilities in all subjects but most profound in mathematics, especially numeric operations. Although many children had cognitive and learning challenges several were able to exceed their expected results for reading, spelling and writing. This finding was very encouraging for future intervention.

There were similarities between the results of this study and those of previous studies, as well as many unique results. Most striking was our higher rate of delay

(27%) and borderline delay (27%). Others have demonstrated mean FSIQ of 94-86 with prevalence of delay between 5% to 24% (Stewart 1989, Wayman 1997, Kennard 1999, Gritti 2001, Krull 2003, Schultz 2003, Adeback 2003). Our cohort had a mean FSIQ of 84 and when combined a mean DQ/FSIQ of 81. These results are more in keeping with recent literature describing a mean FSIQ of 86 (Adeback 2003) than compared to the older cohorts which demonstrated less cognitive delay (Stewart 1989, Kennard 1999). As with Kennard and Stewart's cohort, these patients had greater deficits with math and some language skills, which is in contrast to others who found verbal language impairment (Wayman 1997, Krull 2003). Kennard and Stewart also demonstrated visiospatial and abstract reasoning deficits. Our results seem consistent with the observation that post-transplant patients had difficulty with the higher level abilities of abstract thinking, logical analysis, and flexibility of thought and memory (Stewart 1991, Schultz 2003). This supports the description of greater performance impairment (Stewart 1991). The ability for many of these patients to outperform their expected academic achievement based on FSIQ and school achievement testing is very encouraging for the potential to improve functional outcomes. Most cohorts demonstrated expected or below expected performance but Kennard also found 17 of 28 patients had one subject score greater than their FSIQ and this was predominantly reading (Kennard 1999). Unfortunately, similar to other cohorts, the children we studied were under recognized as learning disabled with only 7 of 30 children receiving early intervention or modified learning environment.

Predictive variables previously implicated as contributing to cognitive/developmental delay have included; anthropometric measures demonstrating

growth failure; low serum albumin; high serum bilirubin; and number of days in hospital during the first post-transplant year (Stewart 1991, Wayman 1997, Krull 2003, Schultz 2003). Our results are similar in that growth failure was associated with impaired PIQ and visual motor integration (Beery) and FSIQ. Weight was not predictive of delay but many recorded weights are not indicative of lean body mass because of the issue of ascites and end-stage liver disease. The unique findings of this study are the distinctive patterns of associated variables with the different areas of cognition VIQ and PIQ. This study is the first to demonstrate an association between the post-transplant variable of elevated calcineurin inhibitors (the mainstay of anti-rejection therapy) and impaired FSIQ and VIQ. Other studies have examined cumulated doses of CI for six months prior to assessment but unlike this study not over the length of graft survival (Kennard 1999).

As this represents the results of a single pediatric liver transplant centre the issues arise as to the heterogeneity of the cohort. To provide a sufficient sample size to assess long-term outcomes and to be able to analyze for potential practice variables we recruited children with different etiologies but the same clinical end-point, infantile onset end-stage liver disease requiring liver transplant. Another point of discussion is that we collapsed the results of three different developmental/cognitive measures into one outcome. This was done because of the inability to have one measure for all the developmental age groups and the good to very good predictive validity of the three measures (Bayley, 1993). Therefore we reported the DQ/FSIQ as a single entity.

Our cohort represents a much more homogeneous group compared to all other studies except for Wayman (1997). Only children with infantile onset liver disease and

early transplantation were recruited. Others utilized patients with far more heterogeneous etiologies of liver failure, which may make it more difficult to assess for predictive variables and to accurately predict outcome for individual transplant recipients. Despite this homogeneity of etiology our patients encompass a variable period of time post-transplant and represent the entire spectrum of the evolution of transplant and post-transplant management at our institution. For example, the routine immunosuppression protocol of cyclosporinA/prednisone/azothioprine (1990-1996) was converted to tacrolimus/prednisone therapy with withdrawal of corticosteroids between 6 to 12 months post-transplant (1997-2001). Other changes have occurred during this time frame including the use of split and living related donor grafts. Despite these significant changes there was no difference in the mean DQ/FSIQ in the patients transplanted 1990-96 versus 1997-2001 (mean DQ/IQ 77 versus 83). To further support the use of patients who are at variable lengths of time post-transplant, we examined the stability of cognitive scores in a subset of patients (time period greater than one year between assessments). The developmental/cognitive results were stable over time as demonstrated by test/retest of 5 randomly selected patients ($p = .091$, time 1 versus time 2, Wilcoxon sign rank test). Therefore in the children tested and retested their scores demonstrated a stable cognitive level.

This study had a small group of four children with biliary atresia and functioning Kasai portoenterostomy to assist in assessing whether delay is associated with liver failure and transplantation and not congenital or early insults. But this small group was not a true control group nor did we seek to have a control group of children. Others have compared liver transplant children with other groups of children with chronic

disease (Stewart 1991, Krull 2003). The lack of controls was a specific choice because we utilized population normative validated instruments. If the goal of transplant is to provide as normal a lifestyle as possible then the reality is that transplant children will be compared to their same age peers in preschool, school and social settings. Therefore we chose to evaluate the children with normative population expectations and not to compare them to children with other chronic illnesses.

Our results demonstrate more profound developmental/cognitive impairment than previous studies but the results are on a more homogeneous cohort so all participants had similar risk factors for growth failure, low albumin, malnutrition, hyperammonemia and frequent hospitalizations. We examined children who were infants with a life threatening chronic disease during the time of greatest neural growth, so the magnitude of our results compared to previous studies is not surprising.

Growth failure in these children often encompasses not just linear growth and weight but also head growth. Unfortunately only a minority of patients had a head circumference recorded in the database and therefore we were unavailable to use this in our retrospective study. Granthum-Mcgregor's (1995) review notes that school age children who suffered from early childhood malnutrition have generally been found to have poorer cognitive scores and function, school achievement and greater behavioral problems than matched controls and to lesser extent siblings. There is no consistent evidence of a specific cognitive deficit secondary to malnutrition but the many types of deficiencies can produce different growth and behavioral effects, such as zinc, manganese, copper, iron, protein and energy deficiency. Due to the weight of evidence that malnutrition does effect cognition we postulated that growth/nutrition would be an

associated factor in our results. It was interesting that is was primarily a factor for performance IQ.

The biological plausibility of elevated serum ammonia levels resulting in CNS side effects has been studied extensively. Ammonia toxicity has been demonstrated to correlate with hepatic encephalopathy and the increasing serum levels do have a positive correlation with increasing encephalopathy (Ong 2001). In experimental animal models, ammonia toxicity appears to place an oxidative stress and disturbance in the brain mitochondria bioenergetics. These changes result in astrocyte swelling (Roa 2003). These changes are not just with acute hyperammonemia but can occur with chronic end-stage liver disease and its associated hyperammonemia. Chronic encephalopathy's histological findings demonstrate Alzheimer's type II astrocytes in the grey matter (Gijtenbeck, 1999). Low grade hyperammonemia as seen with extrahepatic portal hypertension has been demonstrated to result in subtle learning deficits. These findings have also implicated motor skills as being affected (Whittington, 2004).

The putative effect of pre-transplant variables have been previously hypothesized (Stewart 1989, Kennard 1999, Wayman 1997). These previous cohorts have demonstrated that poor growth, nutrition and higher serum ammonia are associated with a greater likelihood of mental impairment. But the post-transplant variable of calcineurin inhibitor levels has not been demonstrated as a factor in the past. Certainly there are extensive publications in regards to CNS side effects of this class of medication, but never in the context of cognitive ability. Calcineurin inhibitor neurotoxicity is well known with 40% of patients experiencing these effects (Patchell 1994). The most common clinical presentation is tremor and the classic CI syndrome is

that of leukoencephalopathy of the posterior region of the cerebral hemispheres. This clinically manifests as headache, altered mental status, cortical blindness and seizures. Neuroimaging reveals white matter abnormalities mostly in the bilateral parieto-occipital lobes but also the temporal lobes, pons, thalamus and cerebellum. There has been no study examining correlation of neurotoxicity and any specific cognitive features. Since CI have such diffuse CNS effects it is quite plausible that they are a contributing factor in developmental/cognitive outcome, but further study is required to assess their role in specific patterns of developmental cognitive delay.

The goal of transplantation is to provide an intact survival, which includes health, quality of life, cognitive function and school performance. The concept of intact survival is usually achieved but still requires improvement. Improvement in developmental/cognitive outcome can be achieved with early intervention. (Hack 1999) Further prospective multi-centre research is required to assess the impact of aggressively improving pre-transplant nutrition or earlier liver transplant when the child exhibits growth failure or hyperammonemia or by attempting to achieve a narrower therapeutic window for serum calcineurin inhibitor levels. The most important impact of this study has been to highlight the profound need to objectively assess developmental/cognitive status in all children post-liver transplant as the prevalence of delay and borderline delay is much greater than previously reported. This may be achieved by enrolling all these children in long-term neurodevelopmental follow-up. This may allow us to provide all supports available to maximize their potential and their ability to succeed in school, with peers and into adulthood.

Chapter 5

Objectives 3 and 4

Methods, Results and Discussion

5.1 Methods

This study details the health-related quality of life in children with infantile onset chronic liver disease who were transplanted less than or equal to six-years of age. This study represents a cohort study. Analysis was used to identify modifiable and non-modifiable variables that may contribute to decreased quality of life.

5.1.1 Subjects

Patients with infantile chronic end-stage liver disease who were transplanted at the University of Alberta Hospital between 1990 to 1999 and who continued to receive care in our institution were invited to participate. Subjects were ages 3 to 17 years as the Multi-attribute Health Status questionnaire (MAHS) can be administered from three years to adulthood. Our inclusion criteria required children to be between 3 and 17 years of age. The children transplanted between 1999-2001 and assessed for developmental cognitive status were all less than 3 years of age so were ineligible for this portion of the study. Inclusion criteria for this study included; i) infantile onset of end-stage liver disease; ii) liver transplant $\leq$ 6 years of age; iii) at least 6 months post-transplant.

The reference group is 145 children, who were eight years old and students of the Hamilton-Wentworth Roman Catholic Separate School Board (Saigal 1994). The results of this reference group have been previously published and cited (Saigal 1994 and Midgley 1999).

5.1.2 Measurement

Families were contacted prior to their annual liver transplant follow-up or were registered during their immediate post-transplant course for follow-up at one year. The questionnaire was proxy administered to primary care givers who accompanied the patients for their annual evaluations. Although some patients were old enough for self-administration, to provide consistency a proxy was utilized for all participants.

The questionnaire was administered by a face-to-face interview conducted by one research nurse. The attributes of self-care and cognition may be difficult to interpret for pre-school aged children. The administrator of the questionnaire has had extensive experience in developmental pediatrics and could provide information on age-appropriate personal-social standards.

Standardized HRQOL Measures: Multi-attribute Health Status (MAHS)

The use of standardized valid measures for pediatric HRQOL is not as well established as the standardized measures utilized for developmental/cognitive assessment. Therefore a review of previous studies and questionnaires was required to select an appropriate measure. The measure selected was MAHS.

The MAHS represents one approach to assess pediatric health related quality of life. It includes measuring several dimensions of health simultaneously (Feeny 1995). It can be utilized as a descriptor of quality of life, or when the preference based scoring is applied to the responses, it can provide a utility score. The utility score function is referred to as the Health Utilities Index (HUI). The MAHS is shown in table 5.1. As

noted there are eight attributes that require the respondent to choose one of the four or five responses for each.

The MAHS was originally devised to examine health status of childhood cancer survivors (Feeny 1992). The following six attributes were considered the most important by parents and children during the development of the questionnaire: sensation, mobility, emotion, cognition, self-care and pain. A fertility domain was included in the HUI II because of the effect of chemotherapy but is excluded when applied to non-cancer pediatric populations. The MAHS was modified by the investigators of ELBW children to include the attributes of behavior and general health. (Saigal 1994) Based upon the results of cognitive and school issues post-liver transplant (Stewart 1989, Wayman 1997) the modified MAHS was used for this study. Each attribute has between four and five defined functional levels of severity, ranging from normal function (level 1) to severe dysfunction (level 4 or 5). Although the questionnaire is not long, in its original format MAHS II provides 24,000 unique health states (Feeny 1995). Population surveys reveal that only a fraction of the possible health states are used. Statistics Canada's General Health Survey had a possible 940,000 with the MAHS III and only 950 unique health states in 11,567 individuals were described. Of those, only 12 health states had a prevalence greater than 1% (Feeny 1995).

The MAHS has been validated for children as young as four years of age and has been used for as young as three years of age (Midgley 2000). Descriptions of quality of life using the MAHS have been published for extreme low birth weight (ELBW) survivors and pediatric head injury patients (Saigal 1994, Gemke 1995, Robertson 2001). The MAHS has been used in general health surveys and in population studies of

school-aged children allowing there to be reference normative population values (Furlong 1989, Saigal 1994).

The application of the modified MAHS is used in this study to obtain a description of the quality of life in a cohort of children post-liver transplant. We also wished to assess if there are any variables, modifiable or non-modifiable, that may be associated with or be a predictor of a poorer quality of life post-liver transplant.

Table 5.1 Modified Multi-attribute Health Status classification system

Attribute	Description
Sensation	1 Able to see, hear and speak normally for age
	2 Requires equipment to see, hear or speak
	3 Sees, hears or speaks with limitations even with equipment
	4 Blind, deaf or mute
Mobility	1 Able to walk, bend, lift, jump, and run normally for age
	2 Walks, bends, lifts, jumps, or runs with some limitations but does not require help
	3 Requires mechanical equipment (such as canes, crutches, braces or wheelchair) to walk or get around independently
	4 Requires the help of another person to walk or get around and requires mechanical equipment as well
	5 Unable to control or use arms and legs
Emotion	1 Generally happy and free from worry
	2 Occasionally fretful, angry, irritable, anxious, depressed, or suffering night terrors
	3 Often fretful, angry, irritable, anxious, depressed or suffering night terrors
	4 Almost always fretful, angry, irritable, anxious, depressed
	5 Extremely fretful, angry, irritable, anxious, or depressed, usually requiring hospitalization or psychiatric institutional care
Cognition	1 Learns and remembers school work normally for age
	2 Learns and remembers school work more slowly than classmates as judged by parents and/or teachers
	3 Learns and remembers very slowly and usually requires special educational assistance
	4 Unable to learn and remember
Self-care	1 Eats, bathes, dresses and uses the toilet normally for age
	2 Eats, bathes, dresses, or uses the toilet independently but with difficulty

	3	Requires mechanical equipment to eat, bathe, dress or use the toilet independently
	4	Requires the help of another person to eat, bathe, dress or use the toilet
Pain	1	Free of pain and discomfort
	2	Occasional pain. Discomfort relieved by nonprescription drugs or self-control activity, without disruption of normal activities
	3	Frequent pain. Discomfort relieved by oral medicines with occasional disruption to normal activities
	4	Frequent pain. Frequent disruption of normal activities. Discomfort requires prescription narcotics for relief
	5	Severe pain. Pain not relieved by drugs and constantly disrupts normal activities
Behavior*	1	Generally compliant, attentive during tasks, well-behaved
	2	Occasionally noncompliant, distractible, disruptive
	3	Frequently noncompliant, distractible, disruptive
	4	Requires medication, psychiatric care for behavior
General Health*	1	Generally in good health, limited use of health resources, active
	2	Slightly more than usual illnesses and use of health resources, not very active
	3	Frequent illnesses and use of health resources, frequently tired
	4	Almost always ill, very frequent use of health resources and hospitalizations, constantly tired

Saigal S, Rosenbaum P, Stoskopf B, et al. Comprehensive assessment of health status of extremely low birth weight children at eight years of age: comparison with a reference group. J Pediatr, 1994; 125(3):411-17

Modified from Feeney D, Furlong W, Barr RD, Torrance GW, Rosenbaum P, Weitzman S. A comprehensive multiattribute system for classifying the health status of survivors of childhood cancer. J Clin Oncol 1992; 10:923-8

* additional attributes (not included in system of Feeney et al.)

5.1.3 Predictive Variables

Pre- and post-transplant variables that impact on long-term quality of life were examined. These variables were selected based upon their correlation with liver transplant outcomes (Stewart 1989, Wayman 1997, Alonso 2003, Bucavalus 2003) and clinical hypotheses. Data for these were obtained from charts and the clinical database of the University of Alberta Hospital's liver transplant program. These variables were divided into pre-transplant, peri-operative and post-transplant. Pre-transplant variables included; etiology, age at transplant, and surrogate markers of disease severity including, height and weight percentiles, number of hospitalizations pre-transplant, serum albumin and serum ammonia. Peri-operative variables were major surgical complications and early re-transplantation. Post-transplant variables included number of days of elevated calcineurin inhibitors (defined as a cyclosporin level greater than 450 μgm/l or a tacrolimus level greater than 15 μgm/l), number of significant infections and number of episodes of rejection. Other variables included current socioeconomic status measured by the Blishen Index (1987) and the children's cognitive status as measured by the WPPSI-R or the WISC-III, depending upon the age of the child.

5.1.4 Ethics

Ethics approval for patient contact and evaluation was obtained from the Health Research Ethics Board, University of Alberta.

Primary care providers were contacted prior the their annual/semiannual assessments and the study was explained during a telephone interview conducted by a research nurse. Preliminary consent was obtained at that time and arrangements were

made for the evaluation. Formal written consent and further explanation of the study was provided at the time of MAHS questionnaire administration.

5.1.5 Statistical analysis

The primary outcome measure was the number of affected attributes on the MAHS. Individual attribute results were compared between the cohort and the reference population using the Chi-square statistic. Secondary analysis included the assessment of the relationship between the MAHS score and demographics, pre- and post-transplant variables. Univariate analysis was performed with the MAHS as the dependent variable with the predictive variables of DQ/FSIQ, age at transplant, Blishen Index, height percentile, weight percentile, serum albumin, number of days of elevated CI, number of significant infections, number of surgical complications and number of episodes of rejection. Predictive variables were included in the multivariate analysis if the univariate analysis demonstrated a p value < 0.2. Only variables or combination of variables with a p value of ≤ 0.05 are reported in the final model. Pearson correlation coefficients were used to assess the relationships between continuous variables. All analyses were conducted with SPSS version 12.0.

5.2 Results

5.2.1 Subjects

Fifty-seven children were transplanted during this time period and 20 children met the study eligibility criteria, which included underlying etiology, age, post-transplant period and location of long-term follow-up (providing consistency by using one nurse to administer the questionnaire). Twenty families participated and one family refused, resulting in 95% participation.

The etiology of the liver disease included 15 with biliary atresia (75%), 2 with α-1-antitrypsin deficiency, two with neonatal hepatitis and one with Alagille's disease.

Patients included 15 females and 5 males. The mean age at the time of the study was seven years eight months (range 3 years to 16 years 9 months). The mean age at transplant was 2.7 years (range 4 months to 6 years). The mean time from transplant was 3.9 years (1 year to 9 years). Patient characteristics are presented in table 5.2.

The practice variables of participants are presented in table 5.3. As noted in the table, the patients have an average socioeconomic status with a mean Blishen score of 40.75 (Canadian mean 43). The children were on average about 2.5 years at the time of their transplant and required a mean of 2.65 hospitalizations prior to transplant. They had a mean height and weight percentile of 20% but the median was < 5% indicating growth impairment. Their serum biochemistry evidenced significant liver disease with a decreased serum albumin, mean 27.7 g/l, and elevated serum ammonia, mean 58.9 μmol/l. Post-transplant demonstrated few surgical complications (mean 0.95).

Although the children experienced rejection (mean 1.7 episodes), infections (mean 3.8 episodes) and days of elevated calcineurin inhibitors (mean 7.9 days). Their cognitive status was similar to the n = 30 cohort of children with a FSIQ in the borderline delayed range, 83.

Table 5.2 Patient characteristics for HRQOL study

Sex	15 females; 5 males
SES (mean Blishen score)	40.75 ± 15.42 (Range 21 – 75)
Etiology of liver disease	15 biliary atresia; 5 other
Status at transplant	15 at home; 5 hospitalized
Mean age at transplant	2.76 ± 1.96 years (Range 4 months - 6 years)
Mean time elapsed since transplant	3.9 years (Range 1 – 9 years)

Table 5.3 Practice variables of participants (n = 20)

Pre-transplant	Mean (± SD)	Range
Age at transplant (years)	2.8 years ± 2.0	4 months – 6 years
Height percentile	20 ± 24.0	< 5% -75%
Weight percentile	23 ± 29.8	< 5% - 95%
Albumen g/l	27.9 ± 8.5	15 – 49
Ammonia µmol/l	58.9 ± 64.1	20 - 265
# hospitalizations	2.7 ± 1.7	0 - 5
Post-transplant		
# surgical complications	1.0 ± 1.3	0 – 4
# days of elevated calcineurin inhibitor	7.9 ± 6.7	0 - 21
# infections requiring hospitalization	3.8 ± 4.0	0 -15
# episodes of rejection	1.7 ± 1.7	0 - 7
Intelligence scores	82.6 ± 17.0	51 - 121
Socioeconomic status (Blishen Index)	40.8 ±15.4	25 – 75
(Canadian mean 43)		

5.2.2 MAHS Results

There were 13 unique health states (unique combinations of normal and deficited responses to attributes) to describe 20 patients. The majority, 16/20 of patients, exhibited functional limitation. Most patients had mild limitation with level 2 functioning. Two patients had level 3 function in the attribute of emotion, one patient had level 3 function in the cognitive attribute, another with level 3 function in behavior and one level four function and one patient had level 4 function in self-care.

Post-liver transplant patients exhibit a greater burden in their health status versus a pediatric reference population (Saigal, 1994). Only 20% of transplant patients had unaffected function in all attributes versus 50% in the reference population. Thirty-five percent of patients had 3 or more levels involved versus 2% of reference children (table 5.5).

The attributes that were affected the most were pain 40% (n = 8), behavior 45% (n=9), and emotion 35% (n = 7). Fewer transplant patients were viewed as having behavioral issues versus reference populations (although not significant). Only three families described their child as having diminished general health. (table 5.4)

Table 5.4: % patients with abnormal score on the Multiattribute Health Status Classification System: 20 children after liver transplant at ≤6 years of age, compared to a reference population.

Attribute	% abnormal transplantation children*	Reference Population
	n = 20	%
General health	3 (15%)†	47
Sensation	2 (10%)	11
Mobility	6 (30%)†	1
Emotion	7 (35%)	20
Cognition	6 (30%)	28
Self-care	3 (15%)†	0
Pain	8 (40%)†	9
Behaviour	9 (45%)†	59

* score of 2 or more = abnormal

† denotes difference (<0.05) than reference population

Table 5.5 Frequencies of attributes affected in liver transplant survivors and reference subjects

# affected attributes	Liver transplant survivors	Reference population
0	20%	50%
1-2	45%	48%
≥ 3	35%	2%

5.2.3 Predictive Variables, Correlation/Multiple Regression

Univariate analyses did not demonstrate any variable with a $p < 0.2$ therefore no further multiple regression analyses were needed.

5.3 Discussion

The MAHS questionnaire provided an analysis of the quality of life in a cohort of children post-liver transplant. Results demonstrating that the study patients had a diminished HRQOL compared with the reference population were not unexpected. Only 20% of the transplanted children had no affected attributes versus 50% of the reference cohort. Those having ≥ 3 affected attributes were 35%, over 17 times the reference cohort (2%). It was encouraging to note that most exhibited mild impairment. The majority of children (65%) who reported affected attributes only had 1 to 2 impaired attributes. Most of those were at a level 2, only a level below normal function. Although most exhibit mildly burdened quality of life, it is still concerning, however, that the attribute of pain (40%) remains diminished more than 6-months post-transplant. The attributes of mobility and self-care were also reported as more frequently affected versus the reference cohort. The results of the attribute of general health were very interesting, with only 3 care providers not describing their child's health as "good health".

The quality of life did not correlate with the predictive variables including socioeconomic status or any pre- or post-transplant variable. The lack of correlation included no correlation between the MAHS results and the objective standardized cognitive testing (Wechsler).

The recent development of validated generic pediatric HRQOL measures has resulted in other cohorts of transplant recipients being assessed. (Midgley 2000, Bucuvalus 2003, Alonso 2003). Many studies have collapsed the results of all solid

organ recipients together with liver patients accounting for a small number of the cohort (Apajasalo 1997, Manificat 2003). These studies were not felt to be suitable for comparison to our cohort. In general other studies examining quality of life in liver transplant recipients have been similar, demonstrating a diminished HRQOL compared to normal children. Midgley also utilized the MAHS but utilized a utility score. They demonstrated a utility score of .86, with most patients having two to three affected attributes. Again this was diminished compared to the reference cohort. The purpose of Midgley's study was not to assess the HRQOL per se but to compare the utility score with a physician derived measure of disease morbidity. There were no correlations or predictive variables assessed in this study. The Child Health Questionnaire 50-Parent Form (CHQ-50PF) has been utilized by both Bucuvalus (2003) and Alonso (2003), again both find a diminished quality of life with summary scores comparable to other chronic disorders such as juvenile rheumatoid arthritis, asthma and epilepsy (Alonso 2003). Both studies examined the role of any correlating or predictive factors. Alonso found no correlation with age at transplant, height, weight, albumin, significant complications or number of hospitalizations. Conversely with a larger cohort Bucuvalus (2003) found that younger age at transplant, greater time since transplant, higher maternal education and fewer number of hospitalizations in the preceding year were predictive of improved quality of life. Our cohort did not demonstrate similar associations.

Our results were somewhat similar to previous literature despite the fact that we used a more homogeneous cohort and the MAHS was administered during a clinic evaluation and not as a mail-in questionnaire. Except for Midgley who also used the

MAHS, the other studies administered different measures and so there is some difficulty in comparing our results to those using different measures.

Limitations of this study include the proxy administration. Studies have evaluated the correlation of responses between children and their parents, nurses and physicians. The correlation between parent and child on physiologic issues such as mobility, pain sensation is good but on more subjective issues such as emotion and behavior is weaker (Feeny 1993). Since our population incorporated a group of children for whom it was not valid to self-administer the questionnaire it was elected to proxy administer to all patients to maintain consistency. Also, the reference cohort utilized was not a contemporary control group, rather a published reference cohort of children. The cohort number was small and therefore it is more difficult to state that this represents all children transplanted for chronic liver disease. The cohort size was due to this being a single centre study and in our attempt to create a homogeneous cohort of children old enough to administer the MAHS to.

Overall our results are similar to other summary scores for health-related quality of life measures administered to other chronic pediatric conditions. These children comprise a population who have multiple medical encounters, hospital admissions and include families who have endured the threat of a fatal disorder and now must deal with an ongoing chronic disease. Hospitalizations and medical therapy has been shown to impact on the quality of life (Britto 2002)). Therefore it is to be expected that this cohort would demonstrate a diminished HRQOL. Liver transplantation is accepted therapy and the long-term survival is very good, so having mild to moderately lower MAHS results would not be unexpected.

Cognitive function has been demonstrated to impact emotional status (Adeback 2003) so it was somewhat surprising that it was not significantly correlated. Perhaps with a larger cohort the effect of the impaired intelligence would be noted.

It is interesting to note that 85% of parents described their child as exhibiting level one function in the attribute of general health. Although the rest of our results are similar to other pediatric cohorts with life-threatening illness, this attribute was markedly different in the study patients. Our results demonstrate that most children post-liver transplant are described as having "General good health, limited use of health resources, active". Compare this to the healthy reference population in which only 53% of their parents would describe the child as a level one for the attribute of general health. One postulates that the transplant caregiver's appreciation of what constitutes "good health" in a child with a previous fatal illness is vastly different compared to the general population. The reference point for the care providers of children who previously had multiple hospitalizations may be quite different compared to the general population. Further questioning of care providers about the results would be required.

Why the attribute of mobility is so frequently impaired was not an expected finding as these patients are seen in clinic on a regular basis and no obvious neurologic reason has previously been noted. Also all the patients completed a thorough neurologic examination as part of the study and only one patient was noted to have any abnormal findings. Further questioning of parents is required to discriminate between impaired capacity or over-protective parents preventing their child from achieving their capacity. If these attributes have an environmental

component, then further parental education and reassurance will be required to correct the deficits in these attributes.

Liver transplantation in children is now accepted standard therapy. Over the last 20 years, the techniques and management have been refined to provide good long-term outcomes. It is important that we now shift our focus to evaluate functional outcomes in children who are recipients of a liver transplant so that improvements in these domains can keep pace with the evolving technology. It is gratifying to report that our patients have mildly affected attributes, no worse than other cohorts of children with life-threatening disease and that their caregivers view their global health as "good". If our primary goal was to save the life of a child with end-stage liver disease and our secondary goal was to provide a good quality of life, then we must incorporate evaluation of the quality of life, thus allowing the children and their families to voice their evaluation and use the results to improve the children's quality of life.

Chapter 6

Conclusions and Recommendations

6.1 Conclusions

Examination of the intact survival of children who undergo invasive procedures mandates the objective assessment of developmental/cognitive outcomes and health-related quality of life. Cognition is required to develop and adapt and, if impaired, affects all facets of a child's life. Deficits in mental ability will affect school performance and may impact peer relationships (Hack 1999). School and peers form a large part of a child's world. Families may be very supportive and accepting of lower function but society still compares these children to their peers.

A disease modifying intervention, such as liver transplantation, will only be considered successful by patients and families if it improves health-related quality of life. It is their perception of the results that dictates a significant part of the procedure's success; how the procedure has impacted the patient's social, emotional, health, school and family functioning. Therefore the outcome of HRQOL must be analyzed so that if required protocols and procedures can be modified to improve this outcome just as the technical aspects of transplantation are assessed and modified.

The research studies presented in chapters 4 and 5 demonstrate that end-stage liver disease and liver transplantation are associated with impaired development/cognitive function and health-related quality of life.

6.1.1 Developmental/Cognitive Status

In this study borderline and frank developmental/cognitive delay was demonstrated more than in previous literature (Stewart 1989, Wayman 1997, Kennard

1999, Krull 2003, Adeback 2003). Only 46% of the study population had an intelligence in the normal range, with 27% borderline delayed and 27% delayed. There was no specific pattern of cognitive delay but there were specific learning disabilities when we assessed school performance with the WIAT. Mathematics and especially numeric operations were impaired. Encouraging was the results that many of the children were able to exceed expectations in some areas of language, such as reading and spelling.

There were different variables predictive of performance and verbal IQ. Pre-transplant variables impacted on PIQ, with growth failure and hyperammonemia associated with impaired PIQ. The Beery scale, measuring visual motor integration, also demonstrated the same predictive variables, growth failure and hyperammonemia, associated with a diminished score. The Beery is another measure of performance function. Whereas, the VIQ was impacted by the post-transplant variable of elevated calcineurin inhibitors. The Vineland Adaptive Behavioral Scales, provided insight as to the perception of the primary care giver of the child's social function. It was interesting that the care providers did not interpret the function as significantly impaired as the standardized testing. There was no correlation between the DQ/FSIQ and the Vineland communication domain. It was interesting that the only preserved domain was that of socialization, despite the previous hospitalizations and chronic medical condition.

Cognitive/developmental delay is being underdiagnosed and under treated, as there were very few children who were receiving intervention/special education even though 54% of them were borderline/delayed. Perhaps this is due to different

expectations of a chronically ill child or perhaps this may be because it is less evident with the preserved socialization and language functions.

6.1.2 Health-Related Quality of Life

HRQOL in post-transplant children was diminished in comparison with a reference cohort of Canadian children. Post-transplant children had more affected attributes, although the impairment was moderate, mostly with a level of function one below normal function. These results are similar to those children who have had other chronic/life threatening conditions, such as childhood cancer (Feeny 1992) and extreme low birth weight (Saigal 1994). The most affected attributes were behavior (45%), pain (40%) and emotion (35%). One of the most interesting results was that 85% of care providers describe their child as having good health. Unfortunately there was no correlation with the DQ/FSIQ results and the MAHS or the cognitive domain of the MAHS. Therefore this measurement does not appear to provide a screening tool for cognitive issues in the pediatric population.

Liver transplantation is held out to children and families as a hope for life and a meaningful quality of life. To this end, we must assess all outcomes that are deemed important by society, including health-related quality of life and especially for children, their mental function and school performance. Only upon describing these outcomes and their associated variables can we change and improve the interventions we are offering and our patients and families are accepting.

6.2 Recommendations for Future Research

1. All children who undergo liver transplantation in the preschool years require comprehensive screening of their developmental/cognitive function. Measures utilized should be well validated and accepted measures such as the BSID-II, WPSSI-R and the WISC-III, or more appropriately the newer revised editions. Cognitive impairment is currently under recognized by care providers and educators. Cognitive assessments will allow educators to identify deficits and put into place the resources required to allow all children to achieve their maximum potential.

2. Liver transplantation in the preschool age group comprises many different subgroups of children, such as, fulminant liver failure, infantile onset chronic liver disease and childhood onset chronic liver disease. Multi-centre studies are required to recruit sufficient patients to be able to have enough power to allow for comparison of different subgroups. Demonstrating different cognitive impairment in the subgroups would permit identification of high risk groups. Knowledge of the differing groups at risk for cognitive impairment allows for group specific timing of assessment, measures used for assessment and institution of cognitive intervention therapy.

3. Single-centre studies are underpowered to be able to demonstrate the effect of modifying predictive variables and its effect on

developmental/cognitive outcomes. Multi-centre trials are required to allow for meaningful assessment of modifying predictive variables identified in this pilot data, such as:

-Aggressive nutrition pre-transplant, including the use of total parenteral nutrition

-Early transplantation when growth failure is first evident

-Analysis of micronutrients and essential fatty acids pre and post-transplant and their levels and effect on mental status

-Trials of minimal immunosuppression regimes and the outcome of cognitive status as one of the primary outcomes

4. Health-related quality of life has been demonstrated to be diminished in all pediatric liver transplant cohorts. Unfortunately very few patients and families have had assessment of HRQOL. Therefore all children who undergo liver transplant should have an assessment of HRQOL with a valid pediatric measure. Describing the results of large numbers of transplant recipients and their families will facilitate changes in the pre- and post-transplant protocols.

5. The ability to assess specific liver transplant issues and how they impact HRQOL in pediatric liver transplant recipients is not available with generic pediatric measures. This is the detailed required to direct changes

in clinical transplant practice. Therefore there is a need to develop a disease specific measure for pediatric liver transplant.

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Appendix A

A summary of the cited references in developmental/cognitive outcomes is provided in table 2.1. A description of the papers is provided below.

Schultz KH, Wein C, Boek A, Rogiers X, Burdelski M. Cognitive performance of children who have undergone liver transplantation. Transplant 2003: 75(8): 1236-1240.

This study examined the cognitive status of 29 children in the late post-operative phase, after OLT, performed in a single-centre, University Hospital Eppendorf, Hamburg, Germany. Children at least 3 years post-transplant and between 6 years to 12.5 years were recruited. The cohort included children both with and without chronic end-stage liver disease (i.e. acute liver failure). These children were all assessed with the same intelligence measure, the Kaufman Assessment Battery for Children (K-ABC). This testing assesses a sequential processing scale, a simultaneous processing scale and a nonverbal scale. These scales are based on population normative value of 100 ± 15. The mean of all the cohort scales were below population normative values with the sequential processing scale being the most affected (mean = 90, range 63-109). Age at transplantation was highly negatively associated with achievement ($r = -.57$). Height and weight, a measure of nutritional status, were correlated with cognitive function. The overall correlations found that children transplanted younger and who were better nourished pretransplant had better cognitive performance.

The authors concluded that the cognitive function of children in the late phase post-liver transplant was at the lower end of the norm, with children who had better nutrition and earlier transplant having a better outcome.

Adeback P, Nemeth A, Fischler B. Cognitive and emotional outcome after pediatric liver transplantation. Pediatr Transplant 2003; 7: 385-389.

The aim of this study was to evaluate the cognitive function of 21 post-liver transplant children, from the Huddinge University Hospital, Stockholm Sweden. Evaluation utilized the Wechsler measures (WPPSI-R, WISC-III) to assess cognitive function and the Pier-Harris self concept scale for emotional development. The authors also wished to examine any correlation between patients' cognitive status and emotional state. This cohort included children with and without chronic end-stage liver disease. The mean full scale score IQ was 86.6 with 3 patients qualifying as mentally retarded with FSIQ< 70. The highest score was for vocabulary and the lowest was for coding (non-verbal). All the children with subnormal emotional development also had an IQ < 85.

The authors concluded that there was a high degree of cognitive and emotional problems after liver transplant and that routine evaluation of these outcomes should be mandatory.

Krull K, Fuchs C, Yurk H, Boone P, Alonso EM. Neurocognitive outcomes in pediatric liver transplant recipients. Pediatr Transplant 2003, in press.

This study examined the cognitive outcomes of 15 children between the ages of 4 and 12 years, who were transplanted at the University of Chicago, at least two years prior. These children were compared to age matched controls with the diagnosis of cystic fibrosis. This control population was used because cystic fibrosis is a systemic chronic disease of early onset that may result in growth impairment but has no neurological or cognitive complications.

The neurocognitive measures utilized included measures of intelligence WPPSI-R, WISC-II, achievement testing, Woodcock Johnson Tests of Achievement-R, language, clinical evaluation of language fundamentals, memory, test of memory and learning.

Children who were post-liver transplant scored lower than the children with CF on measures of intelligence (FSIQ 90 Vs 99). Verbal IQ was lower in the transplant children versus the controls (86 Vs 99) and this was more pronounced with the receptive language (82 Vs 95). Language delays were more pronounced in children who had been transplanted at a younger age and required longer hospitalizations. On regression analysis, the laboratory indicator associated with poor verbal IQ was the pre-transplant bilirubin level.

The authors concluded that pediatric liver transplant recipients should be screened for speech/language delay at an early stage so that intervention may be initiated.

Gritti A, Di Sarno AM, Comito M, DeVincenzo A, DePaola P, Vajro P. Psychological impact of liver transplantation on children's inner world. Pediatr Transplant 2001:5;37-43.

This was an evaluation of the psychomotor status in 18 children who had a liver transplant and were followed at the University of Naples. The focus of this study was psychoanalytical, with emphasis on the psychiatric evaluation; maturity of ego, anxiety, depressive feelings and body image. As a part of this study intelligence testing was performed using the Wechsler scales, WPPSI-R or WISC-III, depending upon the age of the child. The mean FSIQ was 91.6, with a range of 70-117. Most of the children demonstrated ego immaturity, anxiety of loss and depressive feelings.

The authors concluded that psychic working through of chronic liver disease and transplant is difficult for children.

Kennard BD, Stewart SM, Phelan-McAuliffe D, et al. Academic outcomes in long-term survivors of pediatric liver transplantation.Develop Behavior Pediatr, 1999;20:17-23.

This is a retrospective analysis of the clinical data on 50 children who received follow-up care at Children's Medical Centre, Dallas. It included children at least 6 years of age and who were at least 3 years post-transplant. The cohort is heterogeneous in regards to the diagnosis that led to liver transplant. It included chronic end-stage liver disease, acute liver disease and functioning liver with tumor. Standardized intelligence measures including the Stanford Binet LM, WPPSI-R and WISC-III were used depending on the age of the child. Academic achievement was assessed with the Woodcock-Johnson Educational Test Battery-Revised, providing

information in the following areas, reading, written language and math. FSIQ scores were significantly below population mean at 86.6. Nine of the 50 children had an IQ considered mentally deficient at < 70. In achievement testing, the area of math and written language were < 1 SD from the mean indicating learning problems. Discrepancies between intelligence and academic performance demonstrated that 22 of the children had learning problems. All of the children who had learning problems and an IQ < 70 were receiving special education but only 38% with an IQ > 70 were receiving or had received any special tuition. Therefore the majority of children with learning problems were not being identified in the school system.

The authors concluded that careful assessment of academic patterns in post-liver transplant children is required to maximize the children's potential to fulfill an independent future.

Wayman KI, Cox KL, Esquivel CO. Neurodevelopmental outcomes of young children with extrahepatic biliary atresia one year after transplantation. J Pediatr 1997;131:894-898.

This study evaluated the mental and motor development of 40 infants from California Pacific Medical Centre, who had the diagnosis of biliary atresia and had their transplant < 2 years of age. Children were evaluated with the BSID-II prior to transplant and a 3 months and one year post-transplant. The average DQ post-transplant was 92.7 with a range of 60-129. One year post-transplant 25% were developing normally, 40% of infants were developmentally suspect and 35% were delayed. The children demonstrated a decline in their development 3 months post-transplant but this recovered to pre-transplant status by one year. Analysis of

developmental domains indicated that expressive language was delayed in 48% of children.

Low albumen levels and poor weight gain pre-transplant were associated with delayed neurodevelopmental outcome. Younger age at transplant (< 6 months of age) and prolonged hospitalizations were also significantly related to delayed neurodevelopmental outcome.

The authors concluded that young children undergoing liver transplant are at risk of developmental delay. Aggressive nutritional support and earlier transplantation may reduce the developmental delay.

Stewart SM, Uaoy R, Waller DA, Kennard BD, Benser M, Andrews WS. Mental and motor development, social competence and growth 1 year after successful pediatric transplantation. J Pediatr, 1989;1114:574-581.

This study was designed to assess changes in mental development, social function and growth one year post-liver transplant. This reports on a heterogeneous cohort of 29/37 children, from the Children's Medical Centre, Dallas, who survived at least one year post-transplant. Cognitive/developmental measures included the BSID-R, Stanford Binet LM, and WISC-R depending on the age of the child. Social competence was assessed with the Personal-Social Scales and Child Behavior Check list once again depending upon the age of the child. Growth measures were obtained with routine anthropometric measurements. Mental Scores did not change from pre-transplant to one year post-transplant. Children who had early onset of end-stage liver disease were more likely to have intelligence delays. The average FSIQ was 94 but seven of the twenty-nine children had a FSIQ < 70.

The authors concluded that children's development remained static post-transplant and that children who had onset of liver disease at less than one-year of age were more likely to be delayed.

Zitelli BJ, Miller JW, Gartner CG et al. Changes in lifestyle after liver transplantation. Pediatr 1988; 82(2): 173-180.

This was one of the early studies documenting the outcome of 65 pediatric liver transplants at the University of Pittsburgh. It examined pre and post-transplant hospitalizations, medications, liver and renal function and cognitive ability. The paper states that the BSID, Stanford Binet LM and the WISC-R were used but results of all the patients are not reported. Proxy markers of school placement, states that 51% of patients were in age appropriate grade and 26% one year below. Five of the children required special education. Descriptive parental observations of the children's pre and post-transplant behavior were noted. This noted a significant degree of over-protectiveness.

The authors concluded that cognitive function did not change and lifestyle improved post-transplantation.

A summary of the cited references in HRQOL is provided in table 2.2. A description of the papers is provided below.

Alonso EM, Neighbors K, Mattson C, Sweet E, Ruch-Ross H, Berry C, Sinacore J. Functional outcomes of pediatric liver transplantation. J Pediatr Gastro Nutrit 2003; 37: 155-160.

The goal of this study was to assess the HRQOL post liver transplant with a validated generic questionnaire, the Child Health Questionnaire-Parent Form 50 (CHQ-PF50). Children who were eligible were those who had been transplanted at Children's Memorial Hospital, Chicago, were 5 to 18 years old and were at least 2 years post-transplant and had returned to the hospital for follow-up that year. The questionnaire was mailed out to 86 patients and 55 completed and returned the questionnaire. Non-responders were more likely to be non-Caucasian and not have private health care insurance. Results of the questionnaire demonstrated that parents viewed their children as having poorer general health than the general population. The parental impact domain also demonstrated a poorer emotional impact scale versus normal values. The only other affected domain was the family activities subscale. Interestingly the transplant families describe a better family cohesion compared to the general population . Predictive clinical variable were examined by multiple regression and there was no significant impact on the CHQ-PF50 score.

The authors concluded that the patients had lower physical function versus the general population and that parents in this sample experienced more emotional stress and disruption of family activities.

Schultz KH, Wein C, Boek A, Rogiers X, Burdelski M. Cognitive performance of children who have undergone liver transplantation. Transplant 2003: 75(8): 1236-1240.

This study was completed to investigate the cognitive status and HRQOL in a group of children from the University Hospital Eppendorf, Hamberg, Germany. Children were eligible if they were between 6 and 12 years of age and at least 3 years post-transplant. The cohort was heterogeneous with patients having multiple diagnosis leading to transplant, this included both acute and chronic liver disease. The authors stated that they used a specific questionnaire for children but did not identify the measure. They assessed four subclass; everyday life, social, psychic and physical function. The authors concluded that post-transplant children experience below average scores for everyday functions and psychic functions but the social and physical functioning domains were normal.

Bucuvalus JC, Britto M, Krug S, Ryckman FC et al. Health-related quality of life in pediatric liver recipients: A single-centre study. Liver Transplant 2003; 9(1): 62-71. The goals of this study were to measure HRQOL in a single centre pediatric liver transplantation cohort, Children's Hospital Medical Centre, Cincinnati, and to attempt to identify any clinical or demographic factors that correlate with HRQOL. Two measures were used the CHQ-PF50 and the Peds QL 4.0. Children were eligible if they were between 5 to 18 years and at least 6 months post-transplant. Seventy-seven children participated.

The Peds QL4.0 demonstrated lower scores compared to the general public across all domains; physical health, emotional functioning, social functioning, school functioning and psychosocial health. The liver transplant cohort had similar scores to children with other chronic illnesses.

For the CHQ-PF50, summary scores for the physical and psychosocial domains were lower than the normal population.

Multivariate analysis of the Peds QL4.0 found age at transplantation was an independent predictor for all summary scores, as was maternal education. Physical health scores were higher in Caucasian children who were younger at the time of transplant. The CHQ-PF50 demonstrated that Caucasian patients with fewer recent hospitalizations and a greater time elapsed since transplant had higher summary scores.

The authors concluded that HRQOL was decreased in a population of liver transplant recipients but was similar to that for children with chronic illness.

Midgley DE, Bradlee TA, Donohoe C, Kent KP, Alonso EM. Health-related quality of life in long-term survivors of pediatric liver transplantation. Liver Transplant 2000;6:333-339.

The purpose of this study was to measure HRQOL in children who were long-term survivors of liver transplant and to pilot the authors' developed 12-point scale that attempts to quantify chronic medical disability. Eligibility required that patients were at least 2 years post-transplant and were still followed at the University of Chicago and not lost to follow-up. Fifty-one children and their families participated in the study. The Health Utilities Index-II (HUI-II) was the measured utilized. The

results were compared to a sample of school age children from the Hamilton-Wentworth region, Ontario. Functional limitations were present in 90% of transplanted children versus 50% in the reference population. The most commonly affected attributes were emotion and pain (53% and 65%). Twenty children (39%) had a functional limitation in sensation. Eleven children (22%) had limitations in cognition.

The mean utility score was 0.86 which was significantly less than the reference population, 0.95.

The re was no correlation between chronic medical disability and HRQOL which surprised the authors.

The authors concluded that the children had mild functional deficits and were compared favorably to children with other serious illnesses.

Apajasalo M, Rautonen J, Sintonen H, Holmberg C. Health-related quality of life after organ transplantation in childhood. Pediatric transplant, 1997;1:130-137.

The aim of this study was to examine HRQOL in heart, liver and kidney transplant recipients from the University of Helsinki. Fourteen survivors of liver transplant, who were greater than 6 months post-transplant and at least 8 years of age were enrolled. The authors utilized 3 validated multidimensional questionnaires, the 17D (ages 8-11 years), 16D (12-17 years) and 15D (16-23 years). The liver cohort consisted of 14 patients only 12 of who were still in the pediatric age groups. Control

patients were utilized for all three age. The pre-adolescents had a score of 0.92 with a control score of .937. Other specific results were not separated from the other solid organ recipients.

The authors concluded that for all solid organ recipients, the occurrence of complications before transplant are crucial to the long-term HRQOL.

Appendix B

1. Bayley Scales of Infant Development (BSID-II), 2nd Edition, 1993 (Bayley 1993)

Purpose: This developmental test for children from two months to 3 ½ years has mental (163 items) and psychomotor (81 items) indices which provide quantitative normalized standard scores, with a mean of 100 and SD of 16. These scores provide a mental developmental index (MDI) and a performance developmental index (PDI). In addition, the Infant Behavior Record, provides a third scale of the BSID by recording the child's attitudes, interests, emotions, energy, activity and tendencies to approach or withdraw from stimulation during the testing. The BSID-II has been considered as the best measure of infant development among the many early childhood development tests.

Reliability: The 1993 standardized BSID-II was developed using 1700 infants and toddlers ages 1 to 42 months considering age, gender, race-ethnicity, geographic region and parent education. In addition data was collected on various clinical special needs groups. Reliability coefficients have been established for the BSID-I administering the test to 1262 normal infants and children. The reliability coefficient for the mental scale range from .8 to .93 (median .88) and for the motor scale from .68 to .92 (median .84). **Validity:** Validity has been measured by examining the results of various clinical groups with known medical issues and medical problems and comparing the results with the 1700 reference children. Validity has also been examined by comparing the results of the BSID-II with other developmental testing. Both measures were administered to the child over a 15 day period and the results compared. This included such tests as, the Stanford-Binet Intelligence Scale (Form L-M) which has concurrent validity (r = .57); the McCarthy General Cognitive

Index, with a correlation coefficient of r = .79; and the WPPSI-R which has a correlation coefficient of r = .73.

The authors state that the "BSID-II is designed to sample a wide array of emergent developmental abilities and to inventory the attainment of developmental milestones. Results from the BSID-II can be used to identify areas of relative impairment or delay to develop curricula for interventions and to assess the outcome of any such interventions (Bayley 1993).

2. Wechsler Preschool and Primary Scales of Intelligence-Revised (WPPSI-R)

Purpose: This is a widely used cognitive testing for children for children 3 years to 7 years. The WPPSI-R was designed to measure performance and verbal abilities as well as more specific skills at the subtest level. It also provides a measure of global intelligence at the full-scale intelligence quotient (IQ) level. One of the recognized values of the Wechsler Test of Intelligence is the IQ consistency, therefore Wechsler measures have universal use and acceptability.

Reliability: Reliability testing was completed on 1800 children, comprising 9 age groups and 200 children in each group. Of these children 51% were female and 49% were male; 50% Caucasian, 25% Afro-American and 25% Hispanic. The reliability of the WPPSI-R is excellent with a coefficient for the verbal IQ (VIQ), performance IQ (PIQ) and full scale score IQ of r = . 95; r = .92, r = .96. Test-retest was performed on 175 children demonstrating VIQ r = .9, PIQ r = .88, FSIQ r = .91.

Validity: Validity testing demonstrating that the measure does provide information on cognitive function has been examined comparing the results of the WPPSI-R with other cognitive tests including the WISC-III. There is very good correlation between the two with the PIQ r = .95, VIQ r = .92, FSIQ r= .85. The predictive validity for future cognitive testing between the WPPSI-R and WISC-III is PIQ r = .8, VIQ r = .81 and FSIQ r = .91.

In addition validity was assessed by applying the WPPSI-R to known special needs groups and the score profiles for special needs groups demonstrated the sensitivity to the expected differences in cognitive achievement.

3. Wechsler Intelligence Scales for Children –Third Edition (WISC-III)

Purpose: This individually administered test consists of subtests that combine to give Verbal and Performance scores as well as Full-Scale scores. Again, one of the recognized values of the Wechsler Tests of Intelligence is the IQ consistency. The IQ means are 100 (SD 15); subtest scores, 10 (SD 3).

There is good evidence to relate cognitive testing results of the WISC-III with academic achievement. Interestingly there is only a moderate correlation between the WISC-III and the school grades (GPA) r = .47.

Reliability: Reliability was completed on a USA standardization sample of 2,200 children, 6 through 16 years stratified for gender, race/ethnicity, geographic region and parent education. It included children only if they could speak and understand English. Seven percent of the sample consisted of children with one or more of,

learning disability, speech-language impairment, emotionally disturbed, physically impaired or in special programs; five percent were in gifted program. Canadian normative data is available with the overall mean being 3.34 points above the normative US sample.

Reliability coefficients are VIQ r = .95, PIQ r = .91, FSIQ r = .96. Test-retest reliability was VIQ r = .9, PIQ r = .86, FSIQ r = .93. Inter-scorer agreement is excellent ranging from 0.9 for vocabulary to 0.98 for similarities.

Validity: Validity has been extensively tested with factor analysis. Validity has also been assessed by examining the correlation between the WISC-III and other educational psychological testing. This has included the Stanford Binet, VIQ r = .75, PIQ r = .8, FSIQ r = .94.

Further validity testing has been analyzed by examining the differences between normative and special needs groups, including mentally retarded, gifted and learning disabled children.

Table B.1 Developmental/Cognitive Testing

MEASURE	AGE	SUBTESTS	STANDARDIZED SCORES
BSID-II	2 months to 2 ½ years	Mental (=developmental quotient) Psychomotor Behavior Record	MDI- mental developmental index (=DQ) PDI – performance developmental index
WPPSI-R	3 to 7 years	Comprehension Information Vocabulary Sentences Similarities Arithmetic Block Design Object Assembly Mazes Picture completion Animal pegs	PIQ – performance IQ VIQ – verbal IQ FSIQ – Full-Scale IQ
WISC-III	6 to 17 years	Information Similarities Arithmetic Vocabulary Comprehension Digit Span	PIQ – performance IQ VIQ – verbal IQ FSIQ – Full-Scale IQ

MEASURE	AGE	SUBTESTS	STANDARDIZED SCORES
		Picture completion Coding Picture arrangement Block design Object assembly Symbol search Mazes	

In addition to developmental/cognitive assessments, further assessment was also performed to acquire more information about the learning profile, school performance and adaptive behavioral function. This supplemental information was obtained using the Wechsler Individual Achievement Test for school performance and the Vineland Adaptive Behavioral Scales.

Wechsler Individual Achievement Test (WIAT)

Purpose: This individually-administered academic test is one of the Wechsler family of tests. It represents a composite of the typical curriculum specifications found across the United States, in reading, mathematics, and language arts. The definition of delay, learning disability differs from cognitive testing with a score less than 85 is defined as a delay in that specific learning domain. So the WIAT provides complimentary information about the cognitive/learning patterns of children.

Reliability: Reliability testing was performed on a standardization sample consisting of 4,252 children, age 5 through 19 years, enrolled in kindergarten through grade 12 in public and private school settings. The sample was stratified for gender, race/ethnicity, geographic region and parent education. The children could speak and understand English. Children receiving mainstream special services were not excluded.

Validity: Validity testing for the WIAT has been achieved comparing the results of the WIAT with the WISC-III and concurrent validity with other commonly administered achievement tests. For the eight-year old children of the normative sample, the correlation between the WISC-III Full-scale score and the WIAT total

composite score is r = .73. Ability-Achievement Discrepancy scores can be calculated using scores from concurrent administration of the WISC-III by examining the ability results of the WISC-II with the child's actual achievement score, WIAT.

At the grade 3 level, concurrent validities with other common individually administered achievement tests including, the Kaufman Test of Educational Achievement, the Wide Range Achievement Test- Revised, the Woodcock-Johnson Psycho-Educational Battery-Revised were .79 to .90.

4. Vineland Adaptive Behavioral Scale (VABS)

These scales are individually presented to the child's parent or guardian in a semi-structured interview format in order to assess social competence. Standardization from birth to 18 years 11 months took place on 3,000 US individuals with stratification by sex, race or economic group, geographic region, community size and parent" educational level. The over all mean is 100 (SD 15) with some fluctuation from age group to age group, particularly those including cognitively delayed individuals. The VABS is often used to complement intelligence scales and to provide planning for individual, educational, habilitative and treatment programs because of its strengths of assessing personal and social sufficiency.